> *isolation from tar of pure compounds which were capable of inducing malignant disease of chemicals, and led to the isolation from tar of pure compounds which were capable of inducing malignant disease (Cook and his co-workers).*

As explained by Dr. Rhoads, the Yamagiwa study made clear to cancer researchers and industrial toxicologists that animal studies could be conducted to test carcinogens prior to the observation of disease in humans. Before the Yamagiwa study, cancer scientists could only wait decades until a significant amount of workers developed cancer. But the human-carcinogen link was further obscured by the fact that chemical companies were not conducting epidemiologic studies, so the incidence of human cancer would not be detected until the number of workers with tumors was extremely high.[2] After the Yamigiwa study, the chemical industry realized that carcinogenicity could be tested for relatively quickly because chronic animal cancer studies only take 1–2 years versus, as opposed to decades in human populations.

By the early 1930s, the chemical purification of coal tar compounds was largely completed, and the benzene-based chemical constituents were isolated. Benzene-based compounds (or, to use Rhoads' terminology, "benzene rings linked together") were the key targets for cancer testing:[13]

> *As soon as these investigators had isolated one such substance, they immediately began to create, in the laboratory, many synthetic compounds structurally allied to it. This was done in an attempt to ascertain what peculiarity of chemical structure was responsible for the pathogenic effect. They found that, whereas no absolute rule could be laid down, most of the active substances produced were composed of benzene rings linked together* [emphasis added], *and whereas some modifications did not seem to impair activity, others, though very slight, removed completely the effectiveness.*

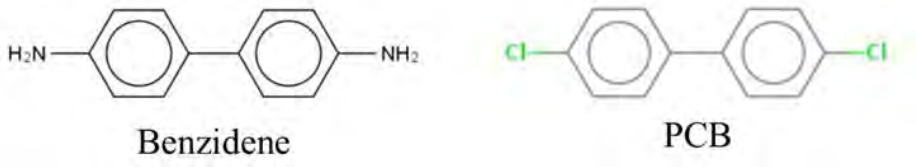
In 1938, Dr. Hueper, a pathologist at the DuPont Haskell Laboratory of Industrial Toxicology, published a study finding that azo-dyes and other *structurally similar* chemicals were carcinogenic. That azo-dyes were carcinogenic was of no surprise; according to Hueper, azo-dyes were discovered to be carcinogenic in humans as early as 1895.[2] What was new about his study was that he identified other compounds having similar structures were also carcinogenic.

In addition to azo dyes, Hueper studied a number of other chemicals *based on their structural similarity to azo dyes.* In fact, he stated that the use of animal cancer studies enabled him to discover two additional azo dyes that had *not* yet been shown to cause cancer in humans. Thus, the trigger for the new compounds was the *chemical structure* of the known azo dye carcinogen that had already been catalogued.[4]

Further, in discussing his findings from the animal cancer tests he conducted, Hueper concluded that benzidine was a potential carcinogen. He tested benzidine because he identified it as a good candidate for being a carcinogen based on its chemical structure. The relevance of this finding is that benzidine is structurally similar to PCBs (Exhibit 1).

[4] Compounds that were found to be carcinogenic were cataloged, so when newly synthesized chemicals were produced by industry, they could be compared with the long list of known carcinogens.

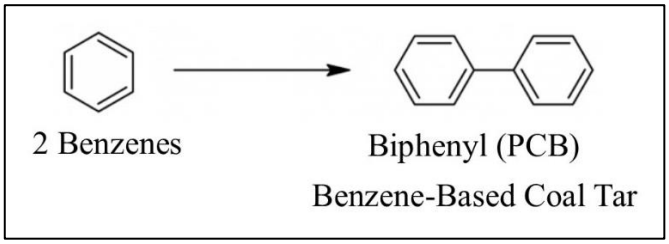
Exhibit 1. Structural Similarities Between Benzidene and PCB



Benzidene PCB

In addition, the backbone of the PCB molecule is the biphenyl ring, which is a benzene-based compound. Exhibit 2 presents the chemical steps necessary to synthesize the biphenyl ring, in which two benzenes are linked together to make one biphenyl ring structure:

Exhibit 2. Chemical Synthesis of a Biphenyl Ring Structure



Given the structural similarity between benzidine and PCBs, Dr. Hueper's findings would have put a reasonable toxicologist on notice that PCBs should be the subject of animal cancer tests. Of note, Hueper's study was published in the same journal (Journal of Industrial Hygiene and Toxicology) and in the same year as the Bennett et al. study involving PCBs.[14]

As previously discussed, the benzenes that Monsanto used in the first step of making PCBs were actually derived from coal tar. Since coal tars had been known to be carcinogenic, this alone should have been a trigger for testing. However, another trigger that was identified at the time was the isolation of pure *biphenyls* from coal tar. That is, by 1927, biphenyls were shown to be part of the coal tar brew of chemicals. Therefore, it was known by 1927 that coal tar caused cancer and that both benzene and biphenyls were chemicals found in coal tar. This, in itself,

should have constituted a trigger since PCBs are biphenyl compounds. For example, Marsh and Simpson showed as early as 1927 that diphenyls (a term that is synonymous with *biphenyls*) made up a fraction of coal tars, which they presented in Exhibit 3.[15] As shown below, diphenyls were listed as one of the 11 hydrocarbons that were known constituents and derivatives of coal tar:

Exhibit 3. Table I from Marsh and Simpson (1927), Constituents and Derivatives of Coal Tar: Hydrocarbons[15]

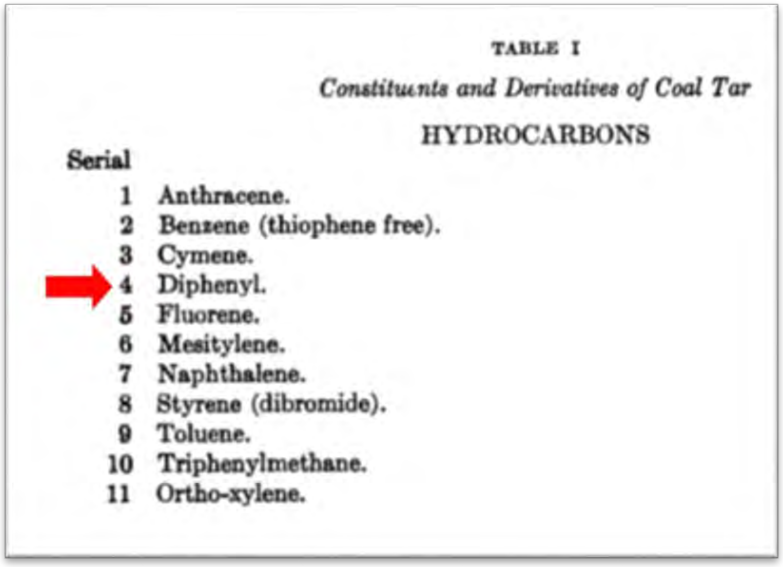


TABLE I

Constituents and Derivatives of Coal Tar

HYDROCARBONS

Serial	
1	Anthracene.
2	Benzene (thiophene free).
3	Cymene.
4	Diphenyl.
5	Fluorene.
6	Mesitylene.
7	Naphthalene.
8	Styrene (dibromide).
9	Toluene.
10	Triphenylmethane.
11	Ortho-xylene.

Through my review and analysis of historical cancer studies, I have observed that the 1930s and 1940s were the most prolific period of cancer testing in the history of toxicology. It should be noted that cancer studies conducted in the 1930s have stood the test of time. The coal tar chemicals identified as carcinogens in the 1930s are still known today as carcinogens.

The most widely used toxicology textbook at both the undergraduate and graduate level is Casarett & Doull's Toxicology: The Basic Science of Poisons, by Curtis Klaassen. The textbook includes a chapter on "Chemical Carcinogenicity," within which there is an extensive section on "Organic Chemical Carcinogens," demonstrating the history of cancer testing on coal tars and benzene-based compounds.[16]

CARCINOGENESIS BY CHEMICALS

By the turn of this century, studies in humans showed that environmental and possibly internal chemical agents are causative factors in the development of cancer (Shimkin, 1977; Lawley, 1944). However, a systematic study of the mechanisms of chemical carcinogenesis was not possible without defined experimental systems. In 1915, the Japanese pathologists Yamagawa and Ichikawa (1915) described the first production of skin tumors in animals by the application of coal tar to the skin. These investigators repeatedly applied crude coal tar to the ears of rabbits for a number of months, finally producing both benign and later malignant epidermal neoplasms. Later studies demonstrated that the skin of mice is also susceptible to the carcinogenic action of such organic tars. During the next 15 years, extensive attempts were made to determine the nature of the material in the crude tars that caused malignancy. In 1932 Kennaway and associates reported the production of carcinogenic tars by means of pyrolysis of organic compounds consisting only of carbon and hydrogen (Kennaway, 1955).

The next section continues:

Organic Chemical Carcinogens

In the early 1930s, several polycyclic aromatic hydrocarbons were isolated from active crude tar fractions. In 1930, the first synthetic carcinogenic polycyclic aromatic hydrocarbon was produced (Miller, 1978). This compound, dibenz-(a,h)anthracene (Fig. 8-1), was demonstrated to be a potent carcinogen after repeated painting on the skin of mice. The isolation from coal tar and the synthesis of benzo(a)pyrene (3,4-benzpyrene) were achieved in 1932. The structures of several polycyclic aromatic hydrocarbons are shown in Fig. 8-1. Polycyclic hydrocarbons vary in their carcinogenic potencies; for example, the compound dibenz (a,c)anthracene has very little carcinogenic activity, while the a,h isomer is carcinogenic (Heidelberger, 1970). The more potent polycyclic aromatic hydrocarbon carcinogens are 3-metholcholanthrene and 7,12-dimethylbenz(a)anthracene. The carcinogenic dibenzo(c,q)carbazole, which has a nitrogen in its central ring, is also considered to be in this class of compounds. Benzo(e)pyrene is reportedly inactive in inducing skin cancer in mice but can "initiate" the carcinogenic process. Perylene is inactive as a chemical carcinogen, whereas chrysene may have slight carcinogenic activity…In 1935,

> *Sasaki and Yoshida opened another field of chemical carcinogenesis by demonstrating that feeding of the azo dye, o-aminoazotoluene (3-dimethyl-4-aminoazobenzene) (Fig. 8-2), to rats can result in the development of liver neoplasms. Similarly, Kinosita (1936) demonstrated that the administration of 4-dimehylaminoazobenzene in the diet also causes neoplasms in the liver. A number of analogs of this compound were prepared and tested for carcinogenic potential.*

Note, the chemicals listed in this excerpt are all benzene-based compounds, and this description demonstrates that benzene-based compounds triggered cancer testing in animals in the 1930s.

2.2.2. Numerous unique and early hallmarks of cancer in the animal studies should have triggered animal cancer studies by as early as 1938.

I base this opinion on two highly detailed pathological studies that were published in peer-reviewed scientific journals: Bennett et al. in 1938 and Miller in 1944.[14], [17] In both of these studies, early hallmarks of cancer were reported in both the liver and blood cells (lymphoma). Despite these early reports of the characteristic of the early stages of cancer, it took Monsanto approximately 30 years from the time these cancer hallmarks were first brought to light for Monsanto to perform long-term cancer studies in 1970.

By 1944, the Bennett and Miller studies had reported specific and unique pathological lesions produced by PCBs in the liver. These lesions were early pathological signs of cancer following PCB exposure that were well known by 1938, when the first PCB study was published by Bennett.

By 1944, the following early pathological lesions—seen at the beginning of tumorigenesis—were reported by both Bennett et al. and Miller:

- Hyaline bodies (unique damaged liver cells) which are seen in cancerous liver tissue;
- Evidence of a large number of mitotic figures and areas of hyperplasia (abnormal cell division) of liver cells;
- Bile duct hyperplasia (abnormal cell division of cells lining the bile ducts; can progress to cholangiomas); and

- Lymphoid hyperplasia follicular lymphoid hyperplasia (abnormal cell division of white blood cells).

I provide a more thorough discussion in Sections 4.2 and 4.3 of the Bennett and Miller studies and the above-referenced indicators.

2.2.3. ***Studies showing DDT as toxic and a carcinogen should have triggered similar studies for PCBs.***

In this section, I extend my historical reconstruction of DDT studies to include toxicity studies that had amassed by 1950. By this time point, scientists had confirmed that DDT was not only toxic but that it was also carcinogenic. These studies were a foreshadowing of the similar PCB toxicity that Monsanto would describe in its own PCB toxicity studies, which it was reluctant to start until 1969. Indeed, the 1945–1950 DDT studies established a pattern of toxic effects that would similarly be described for PCBs in the 1970s. Monsanto, as a manufacturer of both PCBs and DDT, [5] must have known that DDT and PCBs had similar (but not identical) chemical structures, and should have predicted similar toxicity based on the structure-activity relationships.[6]

Between 1945-1950, a number of well-conducted subchronic and chronic toxicity studies were also being published for DDT, showing toxic effects. In 1946, the FDA's Fitzhugh and Nelson (1946) published a 2-year lifetime animal DDT study that found that DDT was a liver carcinogenic and that tumorigenesis followed a dose-response relationship. Fitzhugh and Nelson explained that a long-term study, rather than a short-term study, was appropriate for DDT since it was lipophilic and bioaccumulative (like PCBs).

> *Recent studies on the pharmacology of DDT have treated with short-term toxicity experiments on mammals, with its storage in animal tissues, and with its excretion. No*

[5] According to Monsanto's website, it produced DDT from 1944 to 1957. (https://monsanto.com/company/media/q/what-is-monsantos-opinion-on-agent-orange-and-ddt/)
[6] Monsanto's corporate representative has testified that Monsanto knew the chemical structure of DDT and PCBs when it began making the chemicals. Kaley deposition, *Colella v. Monsanto*, 11/17/2011 (HARTOLDMON0000190-191)

> *study of the lifetime effects of DDT on laboratory animals has been reported. Since long-term feeding experiments with other substances in this laboratory have revealed deleterious effects which would not have been seen in experiments conducted for shorter periods of time, it seemed advisable to feed DDT for the lifetime of the rat.*

Fitzhugh and Nelson noted that it was the chronic bioaccumulation of small amounts of DDT that were hazardous and caused the toxicity—which is precisely the hazard reported for PCBs in later years. In addition, one of the most outstanding gross pathological changes was increased liver weight; Drinker made this same observation regarding PCBs years earlier, in 1937. Furthermore, Fitzhugh and Nelson's summary regarding DDT toxicity presents finding similar to those regarding PCBs in that hepatic cell hypertrophy and tumors developed in a dose-response relationship. This study on DDT should have triggered Monsanto to conduct long-term toxicity studies on PCBs in the mid-1940s.

In 1947, Cameron and Burgess published their findings from numerous types of toxicity investigations that began in 1943.[18] In one of the first highly detailed assessments, Cameron and Burgess investigated both acute and repeated exposure to DDT in different pesticide formulations and routes of exposure. These were rather complex experiments that involved gross observations during necropsy, as well as light microscopy pathological examination (primarily liver lesions). They stated:

> *The introduction of the new synthetic insecticide 2,2-bis (p-chlorphenyl) 1,1,1-trichlorethane (D.D.T.) demands that possible hazards to man be determined and potential dangers safeguarded against. We describe in this paper investigations on the toxicology of D.D.T. which we carried out during the period April, 1943, to March, 1945. These have been the subject of several reports to the Ministries of Production and of Supply, at whose request we have prepared the following account.*

Following pathological examination, Cameron and Burgess found that the liver pathology was prominent and noted that similar pathological lesions that were described in PCB studies by Drinker et al. (1937)[19] and Miller (1944).[17]

In 1948, Fitzhugh once again studied DDT through chronic dosing in rats.[20] And, once again, he stated the importance of conducting chronic studies for highly lipophilic compounds such as DDT because they bioaccumulate with small daily intakes:

> *Because small amounts of DDT in animal food cause the storage of large amounts in animal products which are used in enormous quantities by man, the question of the safety of DDT on and in food products becomes critically important. Experiments with rats fed DDT over a period of 2 years are discussed.*

In this study, Fitzhugh published results from several investigations of chronic dosing in rats, stating that significant liver damage occurs at low exposure levels before any other toxic effects are manifest:

> CONCLUSIONS
>
> *Significant amounts of DDT are stored in the body tissues of animals, especially in adipose tissues, at levels in the diet as low as 10 p.p.m. Histopathological lesions occur in the livers of rats fed 10 p.p.m. DDT in their diet for 2 years. Individual susceptibility to the toxic effects of DDT varies markedly within any given species. Gross effects such as retardation of growth and hyperexcitability do not occur in animals at the low levels of DDT intake which produce significant liver damage.*

In 1950, Laug et al. published a chronic 2-year feeding study in which they exposed animals to DDT levels corresponding to a human dietary level of 5 ppm and found that liver damage occurred even at this low level:[21]

> *It is interesting to note that hepatic cell alterations are seen in greater degree in the male than in the female. This is in contrast to the observation that at higher levels of intake (800 ppm) the female rat is more, rather than less susceptible to intoxication than the male. The finding of hepatic cell alteration at dietary levels as low as 5 ppm of DDT, has*

> *and the considerable storage of the chemical at levels that might well occur in some human hepatic cell alterations occur from diets containing as little as 5 ppm.*

Laug et al. described pathological lesions similar to those reported by Drinker et al. (1937)[19] and Miller (1944)[17] for PCBs:

> *Hepatic cell alterations of a type which in our rats have been characteristic for the chlorinated hydrocarbon on group of insecticides in general and DDT in particular, were noted at the 5 ppm and higher levels, but not at 1 ppm… . The changes consisted of hepatic cell enlargement, especially centrolobularly increase in cytoplasmic oxyphilia with sometimes a semihyaline appearance more peripheral location of tile basophilic cytoplasmic granules.*

In summary, the studies described show that numerous 2-year chronic feed studies had begun by 1943 and were completed and published by 1946. Monsanto could have followed the same toxicity study designs and methods, simply substituting PCBs for DDT. This should have been done given that PCBs and DDT share key characteristics, such as high lipid solubility. The studies published 1945–1950 should also have been warning signs to Monsanto that PCBs could be equally as toxic and carcinogenic as DDT because the pathological lesions reported in numerous studies for DDT were similar to those previously reported for PCB by both Drinker et al. (1937)[19] and Miller (1944).[17] Therefore, Monsanto should have conducted its 1969 study on long-term exposure to PCBs decades earlier.

If Monsanto had conducted long-term, chronic toxicity tests in the mid-1940s, it would have found that PCBs are bioaccumulative, systemically toxic (liver damage), and carcinogenic in laboratory animals carcinogenic--as it did decades later after finally performing such tests.

2.3. Robust Toxicological Testing Protocols for Animal Cancer Testing Had Been in Existence since the Mid-1940s

Well-developed and robust toxicity protocols were developed for undertaking carcinogenicity studies by at least the mid-1940s. Accordingly, if Monsanto had followed these methods during this time period, toxicity tests would have shown that PCBs were carcinogenic. They would have produced similar findings of PCB-induced carcinogenesis in the mid-1940s as they found when they finished their first cancer studies in the early 1970s. In fact, standardized testing protocols had been in existence and presented in Hartwell's 1941 compendium of cancer studies. In this document, he discussed the standard features in the design of cancer studies that are still widely used today in academic and industrial laboratories. For example, his review focused on the following features that still must be considered when designing a cancer study:[1]

- Animal species and strain;
- Animal age;
- Animal sex;
- Animal physical condition;
- Purity of tested chemical compound;
- Doses tested;
- Physical state of compound;
- Route of exposure;
- How chemical compounds were administered;
- Number of study animals;
- Survival rate;
- Duration of experiment;
- Rate of tumors formation;
- Number of tumors

In fact, the National Cancer Institute Hartwell compendium (1941) screened out studies thought to be of insufficient quality or in which the studies could be misinterpreted. In this regard, the document does not include mixtures of chemicals or crude grades of chemicals (where low levels of contaminants could confound the interpretation). It also identifies studies where the data is incomplete and or preliminary. Industrial chemical companies were conducting animal cancer testing, and they were using good standard practices, as I have discussed regarding Hueper's DuPont study.[2]

The protocols that Monsanto finally followed in the early 1970s were similar to those in published literature by the mid-1940s. The vast majority of these early cancer studies cannot be considered slapdash or unreliable. Hartwell (1941) identified the important components of all cancer studies:[1]

> *It is necessary to have a wide range of information in order to designate a compound as carcinogenic or noncarcinogenic. The carcinogenicity of a substance is known to be influenced by many factors, including the genetic constitution of the animal (species and strain), its age and sex, the diet, the physical condition of the animal, the purity of the chemical compound, the dose, the physical state of the compound, the nature of the solvent or vehicle used in administration, the route or site of application. In addition, the value of the results is dependent on the number of animals used, the survival rate, and the duration of the experiment. Thus, the appearance of tumors is dependent to a high degree on experimental conditions, and both the number of tumors and the rate of their appearance are subject to many modifying influences.*

Finally, the following statement by Hartwell could be lifted out of many cancer study protocols being followed today, as there was a concern for both false positive and false negative results:

> *Furthermore, while failure to obtain tumors in a given case may be attributed to conditions of the experiment and should not always be taken to indicate lack of carcinogenic potency, the reports of tumors obtained should also be subjected to scrutiny and not necessarily accepted as proof of such potency. Many tumors are reported with no histologic support of malignancy; many are also reported as caused by the compound under test when only a few tumors are obtained in animal strains of unknown incidence of spontaneous tumors.*

In addition to NCI's Hartwell compendium, many other lengthy lists of animal cancer studies were being compiled during this period, showing that the field of cancer testing had become a very standard practice, even by the late 1930s. The most notable of these include the following:

- A review of the recent literature of tar cancer (1927–1931 inclusive) (Seelig et al. 1933).[22]

- Chemical compounds as carcinogenic agents. First supplementary report: literature of 1937. (Cook and Kennaway 1938.[11])
- Chemical compounds as carcinogenic agents. Second supplementary report: literature of 1938 and 1939. (Cook and Kennaway 1940.[12])

Based on the sheer number and high quality of peer-reviewed cancer studies that were published in the most prestigious scientific journals of the time, a reasonable toxicologist must have been aware of the potential carcinogenicity of PCBs based on the SAR between PCBs and other industrial compounds that were proven to be carcinogenic by the mid-1940s.

3. PRE-1970 TOXICOLOGICAL STUDIES SHOWED PCBS ARE TOXIC AND CARCINOGENIC

I have reviewed the historical peer-reviewed literature during the early years of Monsanto's PCB manufacturing operations to identify a specific time point when sufficient toxicological information was available to unequivocally show PCBs were extremely toxic and could have cancer-causing properties. My conclusions are based on a detailed review of well over 100 historical peer-reviewed scientific publications starting in the mid-1800s through the mid-1940s.

To create a historical timeline of what scientific information was available to scientists at key points before the mid-1940s. I first identified and confirmed several key early hallmarks of carcinogenicity in which scientist used similar toxicological/pathological nomenclature to describe the early stages of tumorigenesis.[14], [17] This formed the basis for constructing a framework of the state-of-the-science to the mid-1940s so that I could determine if the same pathological terminology was used throughout the mid-1800s through mid-1940s. That is, in my research of cancer studies published in the mid-1800s through the mid-1940s, analyzed whether the description of the early hallmarks of cancer were the same or similar to as those reported in the PCB studies. Based on my review and analysis, I conclude that a competent scientist with knowledge of the cancer studies published in the mid-1800s through the mid-1940s (for other chemical compounds) should have concluded that the pathological lesions described by Bennett

and Miller (1938 and 1944) for PCBs should have served as a trigger for Monsanto to initiate 2-year chronic animal studies to determine if PCBs were carcinogenic. I have concluded there was sufficient and compelling pathological evidence by that time to serve as a warning to Monsanto that PCBs were carcinogenic in animals. I further conclude that if they had conducted a 2-year animal cancer study at that time, it would have concluded that PCBs were carcinogenic.

It is important to note that while there are likely in excess of 5,000 toxicity studies on PCBs published to-date, it was not necessary for Monsanto to have conducted a lengthy and complex analysis of hundreds of published studies from obscure and dusty scientific journals by 1944 to have triggered a PCB cancer study. A competent toxicologist reviewing just the three following PCB studies published by 1944 would form a conclusion similar to mine; PCBs were toxic and were animal carcinogens:

- **1936:** Dr. Schwartz. Dermatitis from synthetic resins and waxes. American Journal of Public Health. 1936;26:586–592.[23]
- **1938:** Bennett GA, Drinker CK, Warren MF. Morphological changes in the livers of rats resulting from exposure to certain chlorinated hydrocarbons. The Journal of Industrial Hygiene and Toxicology. 1938;20(2):97–123.[14]
- **1944:** Miller JW. Pathologic changes in animals exposed to a commercial chlorinated diphenyl. Public Health Reports. 1944;59(33):1085–1093.[17]

Dr. Schwartz's study demonstrates early knowledge of PCBs' toxicity. Further, a competent toxicologist reading just the Bennett et al.[14] and Miller[17] studies would be convinced that there was an urgent need for long-term animal cancer studies.

The hallmarks of early stages of tumorigenesis that were reported in the Bennett et al. and Miller PCB studies and should have been regarded as triggers by Monsanto are as follows:

- The unique formation of hyaline bodies in liver cells, which is early evidence of severe damage in liver cells that is associated with liver cancer:
- Extensive liver cell hyperplasia and mitotic figures (unusual number of liver cell divisions) that is associated with regeneration and cancer.

- Bile duct hyperplasia (unusual cell division of liver bile duct cells) that is an early hallmark of bile duct cancer.
- Lymphoid hyperplasia, which is an unusual increased number of white blood cells that can lead to lymphomas.
- Pathological lesions and cellular damage were not repaired after PCB exposures was stopped and animals were allowed to recover for 2 months.

This last finding is particularly important to toxicologists. If the pathological changes seen during PCB exposure had recovered—as would be expected—then a competent toxicologist would conclude that the PCB pathological damage would *not* progress to cancer. However, since there was the unexpected finding that the PCB-induced damage in the liver was *not* repaired, it would have been standard practice for any independent and competent toxicologist to follow the progression of the PCB-induced liver damage in order to determine the eventual outcome of the pathological changes.

The eventual outcome of the early hallmarks of cancer reported in 1939 by Bennett and in 1944 by Miller would ultimately be revealed in the 1970s and 1980s by independent scientists conducting 2-year animal cancer studies. In fact, Monsanto's own first 2-year animal studies completed in the early 1970s showed PCB were carcinogenic in animals (despite the fact that these studies included fraudulent data and information). It is my opinion that if Monsanto had conducted that same 1970s chronic cancer study in the 1930s, 1940s, 1950s, and 1960s, it would have concluded that the lesions reported by Bennett et al.[14] and Miller (1944)[17] were indeed early hallmarks of cancer, and at the end of 2 years, Monsanto would have confirmed evidence of PCB-induced cancers.

Further, it is my opinion that any independent competent toxicologist could have predicted by the mid-1940s, that once PCBs were bioaccumulated, they would not be eliminated easily or rapidly. Thus, it was foreseeable by the mid-1940s that PCBs would bioaccumulate in the food web because PCBs possessed the two most important physicochemical properties: lipid solubility and persistence which I discuss in great detail in later.

3.1. 1936: Dr. Schwartz

Schwartz L. Dermatitis from synthetic resins and waxes. American Journal of Public Health. 1936;26:586–592.[23]

This section presents summary information to support my opinion that an independent competent toxicologist would have known by 1944 that PCBs produce systemic toxicity with the liver being the primary target organ. The toxicological discussion presented by Schwartz (1936) clearly shows that compelling evidence was published before 1944 as he summarized the toxicity as early as 1936.

In 1936, Dr. Louis Schwartz, MD, a Senior Surgeon in the US Public Health Service, published a peer-reviewed study detailing the emerging reports of widespread skin diseases and systemic toxicity among workers who were exposed to chlorinated compounds, including PCBs. While it was widely known that PCBs were causing a specific type of skin disease among PCB workers, Schwartz also reported a case of PCB-related toxicity in the general population—namely, the wife and child of a PCB worker.

The American Journal of Public Health had a wide readership—including industrial hygienists in the chemical industry. It should also be noted that because Schwartz's study results were previously "read" before the Industrial Hygiene Section of the American Public Health Association at the Sixty-fourth Annual Meeting in Milwaukee, Wisconsin, on October 8, 1935 his findings would likely have been well known throughout the chemical industry.

In stating the purpose of his study, Schwartz noted that while dermatitis associated with manufacture and use of "natural resins" was known, reports of worker dermatitis in the manufacture of "synthetic resins" such as chlorinated naphthalenes and PCBs had not been well studied. However, he warned that exposures were increasing due to a greater number of uses of these compounds in applications such as electric insulators, condensers, insulators on electric wires, paints, varnishes, and lacquers. Obviously, the addition of chlorinated naphthalenes and PCBs to "paints, varnishes, and lacquers" could expose the general public to PCBs. Schwartz

presents an informed and detailed discussion of how PCBs were synthesized, and he identified specific production steps in Monsanto's PCB manufacturing process that posed the greatest health risks from exposure. In his opinion, distillers refining Aroclors were particularly at risk:

> *The workers engaged in chlorinating the diphenyl, especially that part of the operation where the crude Arachlor* [sic] *is being re-distilled to remove impurities, are affected with an acne-like condition of the skin.*

The severity of these dermal lesions is described by Shwartz's firsthand accounts of his medical examinations:

> *The fumes of these compounds cause acne on the face and neck and may penetrate the clothes and cause acne like lesions to develop on the covered parts, the shoulders, and the belt-liner and even on the penis. The lesions on the skin resemble acne. They begin as small, pale, elevated papules, many having no openings in them. They develop into hard cyst-like elevations, under the skin, some of which go on to suppuration [discharging pus], forming boils. Some of the lesions also occur at the mouth of the follicles and resemble the comedones [skin eruptions] and pustules of acne vulgaris.*

Although the first appearance of the skin disease may initially appear similar to adolescent acne, the lesions can increase in severity, leading to medically important infections that need intervention. In addition to chloracne, Schwartz described an increasing number of reports of other medical conditions suffered by the PCB workforce:

> *Those working with the chlorodiphenyls [PCBs] have complained of digestive disturbances, burning of the eyes, impotence, and hematuria [blood in urine].*

At the end of his publication, Schwartz made eight specific recommendations to protect workers in the chlorinated naphthalene and PCB industries. He also recognized that workers' wives and children were also being exposed, and he had examined cases where they developed the same toxic effects and medical symptoms as workers. Indeed, his most detailed recommendation focused on protecting workers' family members as evidence seemed to indicate they were much more sensitive to the toxic effects than was the (primarily adult male) workforce.

Schwartz's first recommendation shows the seriousness and gravity of his concerns regarding the toxicity of chlorinated hydrocarbons, as he stated that production should be "totally enclosed" to achieve zero exposure:

> *1. The protection of the workers from the irritating chemicals that compose the resins and waxes from the resins and waxes themselves. To do this, the process should be totally enclosed* [emphasis added]. *If this is not possible, hoods with suction exhaust should be so placed over open processes that dust and fumes are pulled away from the worker and out of the room.*

He made two other recommendations noting (emphasis added) the seriousness of the health threats:

> *7. There should be periodic medical examination of workers to detect cases of dermatitis and workers in chlorinated naphthalenes and diphenyls [PCBs] should be periodically examined for symptoms of systemic poisoning*...[emphasis added].
> *8. Laws should be passed making it compulsory for factories where there are skin hazards to adopt these measures* [emphasis added].

The fact that Schwartz recommended workers in the PCB industry be "periodically examined" for *systemic poisoning* emphasizes that, as early as 1935, he recognized organ damage to be a major health threat. Workers do not need to be "periodically examined" for skin disease. Those suffering from PCB-related skin disease would have been obvious and immediately diagnosed. However, the only medical symptom that would have been recognized (without robust blood and urine analyses and liver function tests) as systemic toxicity was jaundice (yellowing of the skin and eyes). However, by the time the worker presents with jaundice, the liver has undergone significant damage. What Schwartz was referring to then is an examination of systemic toxicity or *organ damage* needing medical attention, intervention and treatment (however, there is no antidote or therapeutic treatment for PCB-related toxicity).

Schwartz highlighted a case in which he examined a worker's wife and child who presented with the same symptoms seen in the workplace (in this case, Halowax). He describes this confirmed non-occupational exposure case involving family members as follows:

> *I have recently seen the wife and child of a worker who had developed comedones [skin eruptions] and pustules from contact with his work clothes which were saturated with halowax and which he was accustomed to wear at home.*

Schwartz did not present additional information about any other medical conditions diagnosed in family members, but chloracne is a sentinel symptom of PCB toxicity that often heralds underlying involvement of the liver. It is unclear whether Schwartz conducted other medical tests or examinations, or whether he followed the medical outcomes of the wife and child. However, these cases seem to have had a great impact on him as a physician, since he prepared the most specific and detailed recommendation intended to protect workers' wives and children from take-home contamination:

> *4. Two lockers should be furnished to each worker. One for his street clothes and one for his work clothes. The lockers for street clothes and work clothes should be in separate rooms, with the shower baths between the locker rooms. The worker coming to work enters the locker room for the street clothes, takes them off, and puts them in the locker and goes into the locker room where his clothes are kept and dons them. From this room he goes to the workrooms through a connecting door. At the end of his shift, he goes through this door to the work clothes locker room, takes off his work clothes and leaves them on the floor or bench to be washed and then goes to the shower baths and bathes and dries. Then he goes to the street clothes locker room, puts on his clothes and goes out of the door leading to the street. It has been estimated at one plant where such a system was instituted that 6 cents a day per worker will take care of furnishing clean work clothes each day.*

These specific and meticulous worker hygiene steps make it clear Schwartz thought that protecting the health of wives and children from PCBs and other chlorinated hydrocarbons was paramount. To suggest such precautionary hygiene practices would seem extraordinary if the toxic effects of PCBs were not, in Dr. Schwartz's opinion, significant.

3.2. 1938: Dr. Bennett

Bennett GA, Drinker CK, Warren MF. Morphological changes in the livers of rats resulting from exposure to certain chlorinated hydrocarbons. The Journal of Industrial Hygiene and Toxicology. 1938;20(2): 97–123.[14]

One of the three "Drinker studies" (published in 1937, 1938, 1939)

In 1938, Dr. Bennett et al. published the first animal study investigating the toxic effects of chlorinated naphthalenes and PCBs in which a thorough pathological examination was conducted. The pathological findings he reported included obvious visible signs that are seen at the beginning stage of cancer. This report described the early hallmarks of tumorigenesis in the liver and it should have been trigger for Monsanto to conduct 2-year chronic animal testing.

This section summarizes a comparative pathological analysis I conducted based on Bennett's reported pathological findings. Based on my analysis, by 1938, an independent competent scientist would have known that PCBs produced unique pathological lesions associated with the incipient stages of cancer and would have concluded further investigations were warranted.

Bennett's study reported the following PCB-related toxicity and the most salient pathological lesions in the liver:

- PCBs caused a severe, painful, and disfiguring skin disease in hundreds of workers exposed to PCBs; at the time, this disease was called chloracne (lesions are called hamartomas).
- PCBs likely contribute to human death caused by liver failure with symptoms of jaundice (accumulation of toxic hemoglobin breakdown products).
- PCBs cause extensive organ damage in the liver, resulting in dramatic pathological increases in liver weight.
- PCBs cause significant hemorrhaging (bleeding) in animal livers.
- PCBs cause liver jaundice in animals, leading to death.

- PCBs cause a unique formation of hyaline bodies that is evidence of severe damage in liver cells and is also an important hallmark of the early stages of cancer.
- PCBs cause extensive mitotic figures (unusual number of liver cell divisions) that can be indicative of the early stages of cancer.
- PCBs cause bile duct hyperplasia (unusual cell division of liver bile duct cells) that is an early hallmark of cancer and can lead to lesions known as cholangiomas.
- Animal livers with PCB-induced pathological lesions and cellular damage are not repaired 2 months after PCB exposure stops and animals are allowed to recover.

Prior to 1935, as indicated by the Schwartz report,[23] it was well established that workers exposed to PCBs suffered from a disfiguring form of a painful skin disease called chloracne. While this particular link between PCB exposure and chloracne was widely known as early as 1937, systemic toxicity involving liver damage was beginning to appear in workers (although Schwartz noted systemic toxicity, he did not discuss any specific cases).

In 1936, three workers exposed to chlorinated naphthalenes and Monsanto's Aroclors developed severe liver damage while working in the New York Halowax Corporation facility—a condition that ultimately proved fatal. Upon medical presentation, the most obvious symptom was acute jaundice (yellow skin and eyes), and these deaths were the first documented fatal cases associated with exposure to chlorinated compounds. Jaundice was confirmed on autopsy, causing alarm and panic in the chemical industry. These three deaths formed the impetus for Halowax Corporation to seek outside academic consultation to investigate how the chlorinated compounds caused jaundice leading to death.

Although it was obvious the chlorinated compounds were the chemicals causing the three Halowax workers' deaths, the toxic pathological sequelae leading to liver damage were unknown. To investigate the triggering events in the liver and subsequent etiology to explain how these compounds could result in death, Halowax retained the services of Dr. Cecil K. Drinker at Harvard University, School of Public Health, and his colleagues (Drs. Madeleine Field Warren and Granville A. Bennett). Drinker was tasked with elucidating the cellular liver damage and determining how the chlorinated compounds caused such severe cases of jaundice. It

should be noted that since Drinker was charged with determining exactly how the chlorinated compounds Halowax was using in its operations caused jaundice, he formulated the same chlorinated mixtures that workers were being exposed to inside the Halowax facility. In other words, Drinker and his colleagues followed an *applied toxicology* study design using the actual workplace mixtures, rather than a *research toxicity* study that would have focused on individual pure chlorinated hydrocarbon compound mixtures. Following the completion of its experiments, the Drinker team reported its findings in the following three peer-reviewed published studies (collectively, I refer to these as the *Drinker studies* in this report):

- Drinker CK, Warren MF, Bennett GA. The problem of possible systemic effects from certain chlorinated hydrocarbons. The Journal of Industrial Hygiene and Toxicology. 1937;19(7):283–311. (Minutes from the 1938 Drinker conference at Harvard University are presented at the end of this report.[19])
- Bennett GA, Drinker CK, Warren MF. Morphological changes in the livers of rats resulting from exposure to certain chlorinated hydrocarbons. The Journal of Industrial Hygiene and Toxicology. 1938;20(2): 97–123.[14]
- Drinker CK. Further observations on the possible systemic toxicity of certain of the chlorinated hydrocarbons with suggestions for permissible concentrations in the air of workrooms. The Journal of Industrial Hygiene and Toxicology. 1939;21(5):155–159.[24]

Drinker also prepared the following private report to Monsanto:

- Drinker CK. Report to the Monsanto Chemical Company. September 15, 1938.[25]

In 1937, Drinker also chaired a one-day conference at the Harvard School of Public Health (herein called the *Drinker Conference*) to present his findings on the "systemic effects" of chlorinated naphthalenes and diphenyls (PCBs). Following his presentation, further discussions were held among other attendees, including representatives from Halowax Corporation, Monsanto Chemical Company, General Electric, the US Public Health Service, state health officials from Massachusetts and Connecticut, and others (meeting minutes included at the end of the 1937 Drinker study).

I have reviewed the Drinker studies and the conclusions of my analysis is that the PCB-induced toxic damage to the liver observed in Drinker's animal studies was consistent with the autopsy reports cause of death. Its conclusion was that Halowax workers died of acute liver damage. Although the Halowax workers were exposed to a mixture of chlorinated naphthalenes and Aroclors, Drinker's findings revealed for the first time that Aroclors were actually more toxic than chlorinated naphthalenes. It was not possible to attribute specific contributions of the chlorinated compounds in the mixture to the liver damage but Drinker's finding that PCBs were more toxic than the other compounds is important.

3.2.1. Background and Purpose of the Drinker Studies

In the first 1937 Drinker study,[19] the researchers clearly stated that, due to the extensive use of chlorinated compounds, a great deal of scientific work had been published on chloracne skin disease (as was illustrated by the 1936 Schwartz study[23]), but little research had focused on the systemic effects to the liver. Therefore, their primary goal was to uncover, if possible, how PCB produced toxic effects in the liver and ultimately death:

> *Our investigations have not been concerned with chloracne but with the possibility of systemic effects following ingestion or inhalation of such products.*

As mentioned above, the investigators were prompted to open a new area of study following a direct request by Halowax Corporation to investigate how the chlorinated compounds caused liver jaundice resulting in death:

> *In the spring of 1936, the Halowax Corporation, a division of the Bakelite Corporation, called our attention to three fatal eases of jaundice in workmen using chlorinated naphthalenes and chlorinated diphenyl, and requested that the subject be investigated rapidly and thoroughly as possible.*

A synopsis of patient presentation and autopsy findings were provided for each of the three patients and their exposures. It was noted that only Patient 1, who was exposed to a small amount (10%) of PCBs, developed chloracne, which developed in tandem with liver disease (jaundice). However, there was no chloracne reported for either Patients 1 or 2, who were only

exposed to chlorinated naphthalenes (halowax). This may indicate that the chloracne was only caused by PCBs (not chlorinated naphthalenes).

One other striking difference between the three patients is that only Patient 1, who was exposed to PCBs, suffered from gastrointestinal (GI) tract ailments. No such GI involvement was reported for Patients 2 or 3 (who were only exposed to chlorinated naphthalenes). This seems to confirm the reports by Schwartz, who noted that GI distress was reported with PCB exposures.

Based on the limited medical information provided by Drinker,[19] it appears that Patient 1 (who was exposed to PCBs) exhibited greater systemic organ damage (i.e., skin, GI tract, anemia, and liver) and had more severe symptoms than Patients 2 and 3, who were not exposed to PCBs. In fact, Patient 1 presented with only GI complaints. Only later did he succumb to fatal liver disease.

In brief, summaries of the three patients are as follows:

> *Patient 1. Male. age 21. The previous medical history of this man was in no way significant except for the fact that he had an attack of jaundice about 6 weeks prior to his fatal illness. Late in December, 1936, he became badly constipated and had much abdominal pain and distention. When admitted to the hospital he was slightly jaundiced and was evidently very ill. He was somewhat anemic and his skin, particularly upon the arms, face, chest and back showed many pustules…at autopsy was found to have a cirrhosis of the liver with acute yellow atrophy superimposed upon it. This man had been exposed to low concentrations of vapors arising from a mixture of tetra and pentachloronaphthalenes together with approximately 10 per cent of a refined chlorinated diphenyl. While both he and others engaged in the same work had chloracne…* [emphasis added]
>
> *Patient 2. This was a young man who died in February, 1936, after an acute illness characterized by jaundice. He had been exposed to fumes arising from a mixture of penta and hexachloronaphthalenes. There is no record of chloracne* [emphasis added]. *The patient worked with a large number of other people of whom but one (Patient 3), a close friend, had significant illness.*

> *Patient 3. Another young man employed with Patient 2. He became jaundiced in March, 1936. and died after an illness of 2 weeks. A careful autopsy resulted in a diagnosis of acute yellow atrophy of the liver. Here again no history could be obtained as to a precipitating cause, and there was no record of preceding attacks of jaundice.*

Although this simple comparison of exposure to different chlorinated compounds based on case histories from three patients is not definitive, this comparison does indicate that while chlorinated naphthalenes and PCBs produced similar toxic effects in the liver, PCB toxicity involves more organ systems. This deduction was shared by the President of Halowax, Sanford Brown (patients worked in his Halowax plant), who attended the 1937 Drinker/Harvard Conference and compared the health problems before and after the company started using PCBs together with chlorinated naphthalenes in its manufacturing, stating to the attendees:[14]

> *That is the problem we have had in this case. It [Halowax's chlorinated naphthalenes] has been on the market for 25 years. Until within the past 4 or 5 years there has never been any intimation that it would cause any systemic effects. Thousands and thousands of workmen have dealt with millions and millions of pounds of certain of these materials, particularly the tri-chloranaphthalenes* [sic]. *Then we come to the higher stages, combined with chlorinated diphenyl and other products, and suddenly this problem is presented to us* [emphasis added].

Drinker also noted that "in addition to these three very recent fatalities, we have learned of four other possible cases, none of them fatal."[19]

In the above quote, Mr. Brown (Halowax Corp) stated an obvious but important fact that most scientists would identify as an important anomaly that required further investigation. That is, it is unusual (or suspicious) that Hallowax never experienced any health problems for 25 years and only started seeing health problems when they started using higher chlorinated diphenyls (when workers died). While this *proves* nothing, it should have been a trigger for Monsanto to conduct a similar study using only PCBs—but it did not. Instead, throughout the following years, Monsanto pointed specifically to the Drinker studies as being corrupted and "uncertain" because mixtures of chlorinated naphthalenes and PCBs were used in those studies (Kelly 1950).[26]

While this is true, nothing prevented Monsanto from conducting their own toxicity testing in which animals would be exposed *only* PCBs.

In addressing the systemic toxicity of chlorinated naphthalenes and PCBs, Drinker developed an overall study design to evaluate the toxicity workers could suffer while performing workplace activities in different parts of the plant. That is, because Halowax used different formulations in different areas of the plant, he tested mixtures of chlorinated compounds with which workers would be expected to come into contact. The exact formulations he tested comprised an attempt to reproduce in his animal studies the actual worker exposure conditions in the Halowax plant. His intent was clearly stated, "These preparations were selected because of their relative importance in industry."

This experimental design limits the toxicity information that can be extracted for individual compounds such as PCBs. However, after careful analysis of the types of mixtures Drinker tested and comparing the pathological findings for various mixtures, I can conclude that a reasonable toxicologist studying PCBs would have known the following by 1939, based on the totality of the Drinker studies:

- PCBs and chlorinated naphthalenes both produce severe and widespread liver damage;
- PCBs are more toxic than chlorinated naphthalenes;
- PCBs produce a unique pathological constellation of liver organ damage and cellular pathology that had not been seen before; and
- The liver damage is not repaired after exposure stops and animals are allowed to recover.

Despite these deaths and the possibility that Monsanto's PCBs could have contributed to the cause of death and liver jaundice, Monsanto conducted no additional credible PCB toxicity testing to determine the chronic toxic effects of PCBs for several decades.

In the sections below, I have extracted PCB-specific toxicity information from the Bennett (1938) study because it presents the pathological findings in the most detail.[14] As I discussed above, in trying to recreate the workplace exposure for the workers who died, the team reproduced the mixtures of chlorinated naphthalenes and PCBs, and tested these in rat studies. Although Bennett et al. did not use pure Aroclors in their study, it was necessary to apply a relatively straightforward comparative pathological assessment to extract PCB-specific toxic information.

3.2.2. Chlorinated Compounds Tested by Bennett

Comparative pathological toxicity evaluations are routine and generally used in the field of toxicology when animals are doses with mixtures of chemical compounds. For example, most toxicity testing involves dosing animals with chemical compounds that are dissolved in a solvent (called a *vehicle*). Because the solvent itself may contribute some toxic effect, it is necessary to include a *control* group in which the animal is only given the solvent or vehicle (these are called the control animals). At the end of the investigation, animals receiving the compound are compared to the controls. Such comparative pathological examinations are common, especially when there is concern that the vehicle itself may be toxic.

I have conducted my *comparative* pathological analysis based on Bennett's reported pathological findings for the following compounds he tested, which are as follows:

- Compound A: Mixture of tri- and tetrachloranaphthalenes [sic] (chlorine content, 49.4%);
- Compound B: Mixture of tetra- and pentachloranaphthalenes [sic] (chlorine content, 56.9%);
- Compound C: Mixture of tetra- and pentachloranaphthalenes [sic], plus chlorinated diphenyl (chlorine content, 43.5%);
- Compound D: Mixture of penta- and hexachloranaphthalenes [sic] (chlorine content, 62.6%);

- Compound E: Mixture of penta- and hexachloranaphthalenes [sic] (chlorine content, 62.6%);
- Compound F: Mixture of 90% penta- and hexachloranaphthalenes [sic], plus 10% diphenyl (chlorine content, 63%); and
- Compound G: Chlorinated di-phenyl [sic] (chlorine content, 65.0%).

I noted that while Bennett reported that he had used a "pure" Aroclor (Compound G), he later issued an *errata* clarification indicating there was a mix-up with Compound G. While it was reported in the previous studies that Compound G was a "pure" PCB (Aroclor 1265), Drinker's erratum clarified that the pure PCB tested was not a pure Aroclor, but was a mixture of PCBs and chlorinated diphenyl benzene, stating:

> *The sixth compound has been listed previously as chlorinated diphenyl [PCBs]. It contained 65% of chlorine and proved very destructive to the liver. Later experiments with compound 13 which contained 68% chlorine [Aroclor 1268] and which was also labelled chlorinated diphenyl, were a surprise to us since this second compound was almost non-toxic. On inquiry it was found that substance 6 was in reality a mixture of chlorinated diphenyl and chlorinated diphenyl benzene and that number 13 was actual chlorinated diphenyl.*

To avoid any confusion in my analysis, I have ignored all the experiments and discussions regarding Compound G.

As can be seen in Bennett list of compounds, Compound B and Compound C are very similar; the only difference is that a small amount of PCBs was added to Compound B to make Compound C. In other words, Compound B can be thought of as the vehicle in which Compound C is dissolved (note that the actual amount of PCBs is not presented). With this comparison, it can be determined whether adding a small amount of PCBs either increased, decreased, or had no effect on the toxicity compared with Compound B (the vehicle).

Likewise, a similar comparison can be made between Compounds E and Compound F, since they are identical except for the addition of a small amount of PCBs to Compound E (so it now contains 10% PCBs).

In summary, the comparisons I made were:

- Toxicity of Compound B (vehicle) versus Compound C (containing PCBs); and
- Toxicity of Compound E (vehicle) versus Compound F (containing 10% PCBs).

For the sake of simplicity, I will herein refer to these comparisons as:

- Compound B versus Compound B+PCBs; and
- Compound E versus Compound E+PCBs.

This study design and comparisons of this type are standard practice in toxicology.

My comparative analysis of PCB-induced liver damage is based on the morphological analysis and pathology lesions described by Bennett for each of the compounds noted above. My analysis focused on four toxicity/pathological endpoints that are most often used to score or rank the severity of compound-induced liver damage.

- Liver weight;
- Liver cell (or hepatocyte) damage;
- Presence, absence, or appearance of hyaline bodies; and
- Mitotic figures.

3.2.3. Compound B versus Compound B+PCBs Feeding Experiments

In comparing the pathological changes representing the relative toxicity of Compound B (pure naphthalenes) and Compound B+PCBs (naphthalenes plus PCBs), I should first note that the experiments for these two compounds were feeding experiments conducted with different concentrations (Compound B+PCBs: 3 g/day; Compound C: 0.5/day). Nevertheless, based on his own experiments, Drinker made a final conclusion that Compound B+PCBs was *twice* as toxic as Compound B (no PCBs). Drinker's conclusion was reported in his later table (Drinker

1939),[24] in which his recommended safe airborne concentration for Compound B+PCBs was 0.5 mg/cubic meter compared with twice that level for Compound B, which was 1.0 mg/cubic meter. I briefly describe the differences in the pathological damage between Compound B and Compound B+PCBs for the primary pathological lesions in the following sections.

3.2.3.1. Liver Weight

Liver weight is a sensitive toxic endpoint that is documented in all toxicity studies on the liver. Increases in liver weight indicate general damage has occurred due to liver toxicity/pathological changes induced by exposure to toxic compounds that target the liver.

The comparative pathology showed that Compound B+PCBs caused significantly more damage than did the vehicle (Compound B). For example, Drinker reported that "there were no significant variations in weights" observed with Compound B. However, for Compound B+PCB, Drinker reported that, "In all animals the livers were enlarged (33 to 90 per cent). The average weight increase was 71 percent."

3.2.3.2. Liver Cell Damage

The liver cell damage resulting from Compound B, was described as follows:

> *The majority of the liver cells contained large numbers of small fat vacuoles.*

Liver cells exposed to Compound B+PCBs appeared to have more extensive and different pathological lesions:

> *Practically every liver cell was swollen and rounded. Their cytoplasm contained large numbers of hyaline bodies* [emphasis added]. *These were circular or oval in shape and varied in size from about half the size of a red blood corpuscle to twice the size of the nucleus of a liver cell.*

3.2.3.3. Hyaline Bodies

While no hyaline bodies were mentioned as being formed with Compound B exposure, there was a stark contrast with animals exposed to Compound B+PCB. These unique structures, which are

indicative of severe pathology and are potential hallmarks of early cancer, were obvious, numerous, and uniquely arranged only after Compound B+PCB exposure:

> *In numerous instances, many small hyaline* [emphasis added] *bodies had fused, forming large circular masses as large or larger than a normal cell. These bodies stained brilliantly with eosin dye. They were often laminated and occasionally contained small clear fat vacuoles in the central portions…The most conspicuous feature of these rats was the presence of large numbers of circular hyaline droplets* [emphasis added] *in the cytoplasm of the liver cells…Although similar hyaline droplets* [emphasis added] *were observed in livers of rats exposed to various chlorinated naphthalenes, this type of degeneration occurred much earlier and to a much more marked degree in those rats that were exposed to preparations containing chlorinated diphenyl* [emphasis added]*…"*

3.2.3.4. Mitotic Figures

Following Compound B exposure, mitotic figures were observed:

> *Mitotic figures were present in increased numbers indicating accelerated regenerative activity.*

Similarly, Compound B+PCBs induced a similar change:

> *Mitotic figures in liver cells were sufficiently numerous to indicate an increased rate of regeneration.*

3.2.4. Compound D versus Compound D+PCBs (10%): Inhalation Exposures

This comparison is based on the pathological changes Drinker reported in which both Compound D and Compound D+PCBs were used in *inhalation experiments* using approximately the same dose and dosing regimen (Compound D: 1.16 mg/per cubic meter for 16 hours/day for 134 days; Compound D+PCB: 1.37 mg/per cubic meter for 16 hours/day for 134 days).

3.2.4.1. Liver Weight

Drinker stated the following for Compound D:

There were no significant alterations in the liver weights.

However, rats exposed to Compound D with just 10% PCB exhibited liver weight increases of approximately 20%:

There were no very significant alterations in the weights of livers although the majority were slightly swollen (average of 20 percent increase in weight).

3.2.4.2. Liver Cell Damage

There was a distinct difference in the severity of the cellular changes to hepatocytes with the addition of just 10% PCBs. With Compound D, liver cells showed slight damage:

After the initial exposure period of 37 days there was evidence of slight injury to liver cells which appeared more granular than normal.

In contrast, Compound D+PCBs clearly caused increases in liver weight, with hepatocytes that increased in size:

The observed pathological changes consisted of swelling and rounding of liver cells…

3.2.4.3. Hyaline Bodies

The greatest pathological changes between Compound D and Compound D+PCBs were in the hyaline bodies. After exposure to Compound D, the following observations were made:

The cytoplasm of occasional cells contained small acidophilic <u>hyaline droplets</u> [emphasis added] *and there was a moderate excess of fat in the form of tiny vacuoles.*

In contrast, the following observations were made following exposure to Compound D+PCBs:

The observed pathological changes consisted of swelling and rounding of liver cells accompanied by a definite increase in the prominence of the cytoplasmic granules. <u>Hyaline droplets in the altered cytoplasm were a conspicuous feature</u>. [Emphasis added.]

3.2.4.4. Mitotic Figures

Following exposure to Compound D, there was *no mention* of mitotic figures. In stark contrast, after exposure to Compound D+PCBs, the following statement was made:

> *Mitotic figures were present in abnormally large numbers.*

3.2.5. Compound D versus Compound D+PCBs (10%): Feeding Exposures

In addition to the inhalation experiments described above, Drinker also conducted feeding studies of Compound D and Compound D+PCBs using the same dosing regimen (3 g per day) for both compounds. The survival periods for rats at this exposure were approximately one month for both compounds (Compound D: 33 days; Compound D+PCBs: 35 days).

Drinker noted that both groups of animals were ill during this one-month dosing period. However, there was a distinct difference in the severity of the toxic effects between Compound D and Compound D+PCB. The morbidity of rats in the Compound D+PCB was significantly increased (which is surprising, since only a small quantity of PCBs—10%—was added to their food). In fact, the toxic effects of Compound D+PCBs were so severe that imminent death was such a concern that feeding was discontinued after only *12 days*. This was directly due to the morbid state of the rats.

3.2.5.1. Liver Weight

Dosing with Compound D resulted in "no significant weight variations."

In contrast, all the livers weights were increased with Compound D+PCB. Remarkably, the largest liver had more than *doubled* in size:

> *Macroscopically, the majority of the livers were enlarged, the largest showing an increase in weight of 118 per cent; the average increase was approximately 40 per cent.*

3.2.5.2. Liver Cell Damage

Exposure to Compound D caused some damage to hepatocytes, but these changes were described as follows:

> *...occurring in cells only occasionally with degeneration occurring rarely.*

Macroscopically, "the livers were friable, yellow and mottled" and:

> *Microscopically they showed marked swelling and vacuolization of the cells. There was also complete degeneration of scattered cells. Occasional mitotic figures were observed (see fig. 4, plate II). Suitable stains revealed very marked fatty degeneration. They contained serous precipitate, a few strands of fibrin, and occasionally a few leucocytes* [sic]*...Rarely one observed one or two degenerating within these spaces.*

Exposure to Compound D+PCBs caused similar lesions, but the damage was much greater than that observed with Compound D, and it appeared to be more widespread throughout the liver. In addition, some pathological lesions that were produced by adding just 10% PCBs were not seen in livers exposed only to chlorinated naphthalenes. The damage that was unique to PCB exposures included obvious pitting and a granular macroscopic appearance of the entire liver. At the cellular level, hemorrhage (bleeding) in the liver, inflammation (involving polymorphonuclear leucocytic invasion), and proliferative bile duct cell division (the finding of this hyperplasia is particularly concerning, as it is associated with cancer).

Macroscopically, "All livers were yellow, friable, and many of them were markedly mottled…. In addition, the external and cut surfaces of the livers appeared slightly pitted or granular."

> *Liver cells between such spaces were distorted, swollen, and showed marked fatty degeneration. In these more severely damaged specimens, extensive hemorrhage had occurred (fig. 2, plate VIII)...In many sections the architecture of the liver was so completely altered that it was difficult to recognize the portal areas.*

Most notably, bile duct hyperplasia was also described as follows:

> *Proliferative changes were occasionally observed in the bile ducts. This was indicated by increased numbers of ducts in certain areas and by mitotic figures in the bile duct epithelial cells.* [Emphasis added.]

Drinker also conducted a separate study to investigate the pathological effects associated with a much lower dose for both compounds (0.5 g every second day). While the compounds produced different pathological changes, the overall damage occurred less rapidly and to a lesser degree.

Importantly, however, even with this lower dose, the liver weights of rats treated with Compound D+PCBs increased.

3.2.5.3. Hyaline Bodies

Exposure to Compound D produced the following:

> *Occasional cells contained oval shaped or circular acidophilic hyaline inclusions.*

But exposure to compound D+PCBs led to the following observation:

> *Hyaline droplets in the altered cytoplasm were a conspicuous feature*. [Emphasis added.]

3.2.5.4. Mitotic Figures

There was a large difference between Compound D and Compound D+PCBs in terms of the emergence of mitotic figures. After exposure to Compound D:

> *Occasional mitotic figures were observed.*

This is much different from what was found after exposure to Compound D+PCBs:

> *Mitotic figures were present in abnormally large numbers.*

In addition to these above differences, a major difference between Compound D and Compound D+PCBs was the observation that just 10% PCBs caused hyperplasia in the bile ducts:

Proliferative changes were occasionally observed in the bile ducts. This was indicated by increased numbers of ducts in certain areas and by mitotic figures in the bile duct epithelial cells.

3.2.5.5. Summary

In summary, all the above comparisons show that adding a small quantity of PCBs to the chlorinated naphthalenes caused an overall increase in the severity of liver pathology. This should have been an alarming trigger for Monsanto and prompted it to conduct chronic animal studies.

PCB-induced pathology was observed both macroscopically (i.e., by the naked eye) and microscopically. Based on commonly used indices of damage, damage to hepatocytes was also significantly different between the groups.

My conclusion that PCBs produce more severe and unique pathological lesions than do chlorinated naphthalenes is supported by other scientists who have made similar comparisons.

In 1955, Wolfgang Felix von Oettingen, MD, PhD (National Institutes of Health, US Department of Health, Education, and Welfare, Public Health Service) reviewed the same Drinker studies that I have analyzed and presented his assessment of the toxicity and dangers of PCBs in a book entitled, *The Halogenated Hydrocarbons: Toxicity and Potential Dangers.*[27] This is a very lengthy (more than 400 pages) and complete summary of toxicity information that was available at the time of publication. In sections where he specifically discusses the toxicity of chlorinated naphthalenes versus that of PCBs, the main conclusion reached by Dr. von Oettingen was that PCBs are much more toxic than are chlorinated naphthalenes.

As I noted previously, Monsanto had for many years considered the Drinker studies not pertinent to PCBs because pure PCBs were not tested. In later years, Monsanto referred to the studies as confusing when asked about toxicity information (Kelly 1950).[26] However, von Oettingen's conclusions showed that when the Drinker studies were carefully evaluated in a comparative manner, the systemic toxicity produced by PCBs was clear, severe, and long-lasting. Von Oettingen analyzed the Drinker studies in the same detailed comparative manner I did (he did not

present individual comparisons), but he came to the same conclusion: PCBs are much more toxic than are chlorinated naphthalenes. In so doing, von Oettingen concluded that the Drinker studies provided sufficient and obvious evidence the health threat and danger posed by PCBs.

In comparing the pathological liver lesions resulting from inhaled mixtures of pure chlorinated naphthalenes and chlorinated naphthalenes+PCBs, von Oettingen stated:[27]

> *Drinker, Warren, and Bennett (1937) and Bennett, Drinker, and Warren (1938) studied the toxicity of a mixture of penta- and hexachloronaphthalenes, [pure chlorinated naphthalenes] containing 62.6 percent of chlorine, and a mixture of 90 percent penta- and hexachloronaphthalenes plus 10 percent refined chlorinated diphenyl, [pure chlorinated naphthalenes+PCBs] containing 63.0 percent of chlorine.*

In line with my opinion, von Oettingen concluded that the liver damage from pure naphthalenes was generally limited to "fatty degeneration and centrolobular necrosis:"

> *They found that with exposure of rats to an average concentration of 8.88 mg. per m.^{3} of the mixture of penta- and hexachloronaphthalene [pure chlorinated naphthalenes] ...most of them heavily jaundiced, the livers showing marked fatty degeneration and centrolobular necrosis* [emphasis added] *of the liver cells.*

Von Oettingen contrasted the above description of results following exposure to pure naphthalenes with Drinker's observations after inhalation of chlorinated naphthalenes plus just a small amount of PCBs (10%) in the following description, which indicates a different and more severe pathology:

> *With inhalation of the same mixture and a mixture of 90 percent penta- and hexachloronaphthalene with 10 percent ...the microscopic examination after 6 weeks' exposure showed swelling of the liver cells, excessive granulation, hyaline inclusions, and occasional mitotic figures* [emphasis added].

His overall conclusion is identical to mine:

> *It is, therefore, evident that the toxicity of chlorinated naphthalenes increases with the degree of chlorination and that the chlorinated diphenyls are especially toxic.*

Von Ottingen also reviewed the comparative toxicity between chlorinated naphthalenes and PCBs in the feeding experiments:

> *Feeding experiments with rats receiving about 0.3 gm. of the mixture of penta- and hexachloronaphthalene illustrated also the toxicity of these compounds. The animals sickened and died gradually, and on autopsy they showed injury of the liver. With mixtures of 90 percent penta-and hexachloronaphthalene and 10 percent chlorinated diphenyl the hepatic lesions were extremely severe* [emphasis added]*, which was also the case with the administration of smaller doses (about 0.05 gm.).*

3.2.6. Interpreting Bennett's Findings: Early Indications PCBs Were Carcinogenic

In addition to the *degenerative* pathological lesions, Bennett[14] reported hyperplastic changes (cell division that occurs in cancer) and other features suggesting cancer.

There were three obvious and specific pathological changes reported by Bennett that were known by the time of his publication in 1938 that were hallmarks scientists used to identify the early stages of cancer. These are as follows:

- Bile duct hyperplasia;
- Hyaline bodies (also known as hyaline figures and hyaline inclusions); and
- Mitotic figures.

Although the Drinker studies reported these pathological changes in the livers of rats exposed to PCBs, the studies were stopped well before (at approximately 3.5 months) any well-developed tumors would form (usually not seen before 18 months[28]). However, the appearance of bile

duct hyperplasia, hyaline bodies, and mitotic figures seen so early after rats were exposed to PCBs should have been alarming because these findings were already known to be the first signs of tumorigenesis (see Section 4.2.5 below).

The Drinker studies showed that the PCB-induced liver damage was very severe and—perhaps more importantly—that the widespread pathological lesions were not repaired even after rats were allowed to recover for two months. This unusual finding by itself should have constituted a red flag to Monsanto's toxicologists/industrial hygienists and triggered chronic animal studies. Monsanto did not know the outcome of the damage from the Bennett study, nor did it seem to care about the prognosis because they did not start any experiments to address this specific issue until the late 1960s.

Unfortunately, Drinker did not offer a prognosis of the long-lasting liver damage, which was still quite pronounced when he killed the animals for examination, but he was not asked to offer any opinion since his charge from Halowax was to determine the cellular liver changes that resulted in death. In other words, his assignment was a cause of death study, rather than a cancer study.

Had Bennett[14] extended the PCB exposures in his study to be a chronic lifetime study, it is my opinion that he would have followed the gradual progression of the hyperplastic changes and mitotic figures to areas of hyperplasia to neoplastic nodules and, finally, to well-defined tumors. In fact, some PCB-induced nodules and tumors reported in later chronic animal studies have been so large that they would have been obvious and detected even with the naked eye (macroscopic examination). For example, in the photograph below, Norback and Weltman (1985) showed a very conspicuous neoplastic nodule measuring a little less than half a centimeter that is visible on the bottom of the right liver lobe (located in the red rectangular outline) (Exhibit 4).[28] This nodule would be immediately obvious upon removing the liver at necropsy. Any suggestion that Drinker would not have seen evidence of cancer in 1939 because cancer studies were not sophisticated or that standard cancer testing protocols were not available is simply not tenable. When tumors are visible to the naked eye and develop in animals exposed to PCBs in 2-year rodent studies, even the most basic cancer study would have concluded that PCBs were carcinogenic.

Exhibit 4. Figure 1 from Norback and Weltman (1985), PCB-exposed Rat Liver at 23 Months[28]

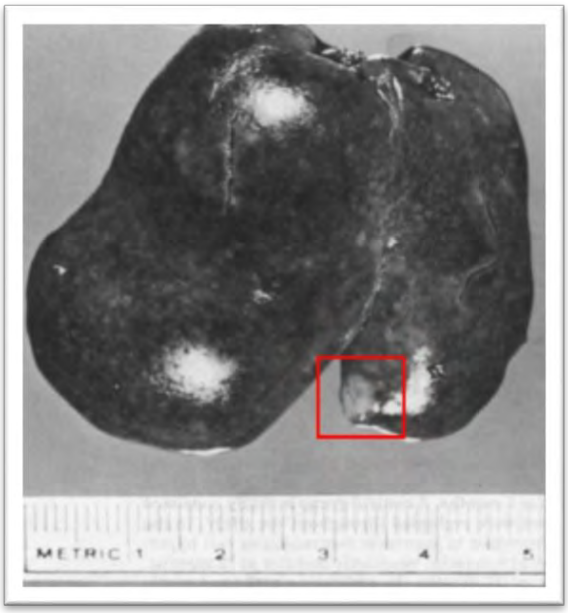


Figure 1. PCB-exposed rat liver; at 23 months. The liver surface is dotted with non-elevated tan foci, .5 to 1 mm in diameter. A neoplastic nodule is present at the tip of one lobe

My opinion that Drinker (or Monsanto) would have found tumors if the study was continued to evaluate lifetime PCB exposures is supported by EPA's analysis of all major cancer PCB studies that were published 1975–1985.[29] In all of these lifetime PCB exposure cancer studies, researchers found a significant statistical increase in the liver tumor incidence rates in lifetime cancer studies. (Note: Although the NCI results were reevaluated and showed fewer tumor rates, Morgan et al. (1931)[30] and Ward (1985)[31] reevaluated the NCI slides for stomach tumors and found 6 adenocarcinomas in 144 exposed rats, which was statistically significant. Furthermore, the tumor rates followed a dose-response relationship (an increase in cancer incidence increased with higher PCB dose levels). The following table from the 1996 EPA report presents the summary results of the tumor incident rates for each study (Exhibit 5).

Exhibit 5. Table from EPA (1996) Liver Tumor Incidences in Rats from Lifetime Exposure Studies, 1975–1985[29]

Table 2–1. Liver tumor incidences in rats from lifetime exposure studies, 1975–1985

Study, sex and strain, mixture	Dose	Original[a]	Reevaluation[a,b]
Kimbrough et al. (1975)	Control	** 1/173 (1%)	** 1/187 (1%)
F Sherman, 1260	100 ppm	170/184 (92%)	138/189 (73%)
NCI (1978)	Control	** 0/24 (0%)	** 0/24 (0%)
M Fischer, 1254	25 ppm	0/24 (0%)	1/24 (4%)
	50 ppm	1/24 (4%)	1/24 (4%)
	100 ppm	3/24 (12%)	3/23 (13%)
NCI (1978)	Control	** 0/23 (0%)	0/23 (0%)
F Fischer, 1254	25 ppm	0/24 (0%)	1/24 (4%)
	50 ppm	1/22 (5%)	2/24 (8%)
	100 ppm	2/24 (8%)	1/24 (4%)
Schaeffer et al. (1984)	Control[c]	** 2/120 (2%)	8/120 (7%)
M Wistar, Clophen A 30	100 ppm	42/130 (32%)	16/128 (12%)
Schaeffer et al. (1984)	Control[c]	** 2/120 (2%)	** 8/120 (7%)
M Wistar, Clophen A 60	100 ppm	123/129 (95%)	114/125 (91%)
Norback and Weltman (1985)	Control	** 0/32 (0%)	0/31 (0%)
M Sprague-Dawley, 1260	100/50/0 ppm[d]	7/46 (15%)	5/40 (12%)
Norback and Weltman (1985)	Control	** 1/49 (2%)	** 1/45 (2%)
F Sprague-Dawley, 1260	100/50/0 ppm[d]	45/47 (96%)	41/46 (89%)

**Statistically significant ($p<0.05$) by Cochran-Armitage trend test (for experiments with more than one dosed group) or Fisher exact test (for experiments with one dosed group).
[a]Hepatocellular adenomas or carcinomas
[b]Decreases between original and reevaluated denominators are due to lost slides; increases, to slides that were excluded originally but could not be specifically identified for exclusion in the reevaluation.
[c]One control group supported both experiments.
[d]Dosing was decreased twice during the study.
Source: Adapted from Moore et al. (1994).

Similar results were found in a 1996 lifetime PCB exposure study that examined multiple Aroclors: 1260, 1254, 1242, and 1016 (a refined 1242 Aroclor). The summary results are shown below (EPA 1996) (Exhibit 6). (Note that there was a gender difference between females and males).

Exhibit 6. Table from EPA (1996), Liver Tumor Incidences in Rats from 1996 Lifetime Exposure Study[29]

Table 2–2. Liver tumor incidences in rats from 1996 lifetime exposure study

Mixture	Dose	Females[a]	Males[a]
Aroclor 1260	Control[b]	** 1/85 (1%)	** 7/98 (7%)
	25 ppm	10/49 (20%)	3/50 (6%)
	50 ppm	11/45 (24%)	6/49 (12%)
	100 ppm	24/50 (48%)	10/49 (20%)
Aroclor 1254	Control[b]	** 1/85 (1%)	7/98 (7%)
	25 ppm	19/45 (42%)	4/48 (8%)
	50 ppm	28/49 (57%)	4/49 (8%)
	100 ppm	28/49 (57%)	6/47 (13%)
Aroclor 1242	Control[b]	** 1/85 (1%)	7/98 (7%)
	50 ppm	11/49 (24%)	1/50 (2%)
	100 ppm	15/45 (33%)	4/46 (9%)
Aroclor 1016	Control[b]	** 1/85 (1%)	7/98 (7%)
	50 ppm	1/48 (2%)	2/48 (4%)
	100 ppm	6/45 (13%)	2/50 (4%)
	200 ppm	5/50 (10%)	4/49 (8%)

**Statistically significant ($p<0.05$) by Cochran-Armitage trend test.
[a]Hepatocellular adenomas, carcinomas, cholangiomas, or cholangiocarcinomas in rats alive when the first tumor was observed.
[b]One control group supported all experiments.
Source: Adapted from Brunner et al. (1996), Keenan and Stickney (1996)

Collectively, the above studies support my opinion that it is more likely than not that an independent and objective scientist conducting lifetime cancer animal studies in 1938 would have concluded that PCBs were carcinogenic.

My opinion is further supported by the Norback and Weltman study, which was specifically designed to follow the pathological lesions from the first month of exposure to the end of the study 24 months later.[28]. The EPA study summarized those findings:[29]

> *Norback and Weltman (1985). Groups of male or female Sprague-Dawley rats were fed diets with 0 or 100 ppm Aroclor 1260 for 16 months; the latter dose was reduced to 50 ppm for 8 more months. After 5 additional months on the control diet, the rats were killed and their livers were examined. Partial hepatectomy (a portion of the liver was removed and examined at different periods) was performed on some rats at 1, 3, 6, 9, 12, 15, 18, and 24 months to evaluate sequential morphologic changes. In males and females fed Aroclor 1260, liver foci appeared at 3 months, area lesions at 6 months, neoplastic nodules at 12 months, trabecular carcinomas at 15 months, and adenocarcinomas at 24 months,*

> *demonstrating progression of liver lesions to carcinomas* [emphasis added]. *By 29 months, 91 percent of females had liver carcinomas and 95 percent had carcinomas or neoplastic nodules; incidences in males were lower, 4 and 15 percent, respectively (see table 2–1).*

In following the progression of the hallmarks of cancer (tumorigenesis), the lesions start as preneoplastic areas (areas of mitotic figures, which were reported in the 1938 Bennett study[14]), progress to nodules, and then progress to carcinomas. This progression is shown in the Norback and Weltman table presented in Exhibit 7.[28]

Exhibit 7. Table 1 from Norback and Weltman (1985), Development of Preneoplastic and Neoplastic Hepatocellular Lesions in Male and Female Rats During Chronic Aroclor 1260 Exposure[28]

Table 1. Development of preneoplastic and neoplastic heptatocellular lesions in male and female rats during chronic Aroclor 1260 exposure.*

	No. of livers with lesions of each three sampled															
	1 mo.		3 mo.		6 mo.		9 mo.		12 mo.		15 mo.		18 mo.		24 mo.	
Lesion	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Focus	0[2]	0	2	2	3	3	3	3	3	3	3	3	3	3	3	3
Area	0	0	0	0	1	0	2	1	0	3	1	3	0	3	3	2
Neoplastic nodule	0	0	0	0	0	0	0	0	0	1	0	3	0	3	1	3
Trabecular carcinoma	0	0	0	0	0	0	0	0	0	0	0	1	0	2	0	2
Adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2

*These lesions were not present in sequentially sampled control liver.

The photomicrograph in Exhibit 8 from Norback and Weltman shows an example of the early cancer hallmarks at 1 month. This is a liver section containing many mitotic figures (in the red area; they describe this as cell hypertrophy). This the same early pathological evidence of mitotic figures reported by Bennett in 1938, where he stated that "mitotic figures were present in abnormally large numbers."

Exhibit 8. Figure 6 from Norback and Weltman (1985), Hypertrophic Hepatocytes Developed in the Central Lobular Region of the Liver at 1 Month[28]

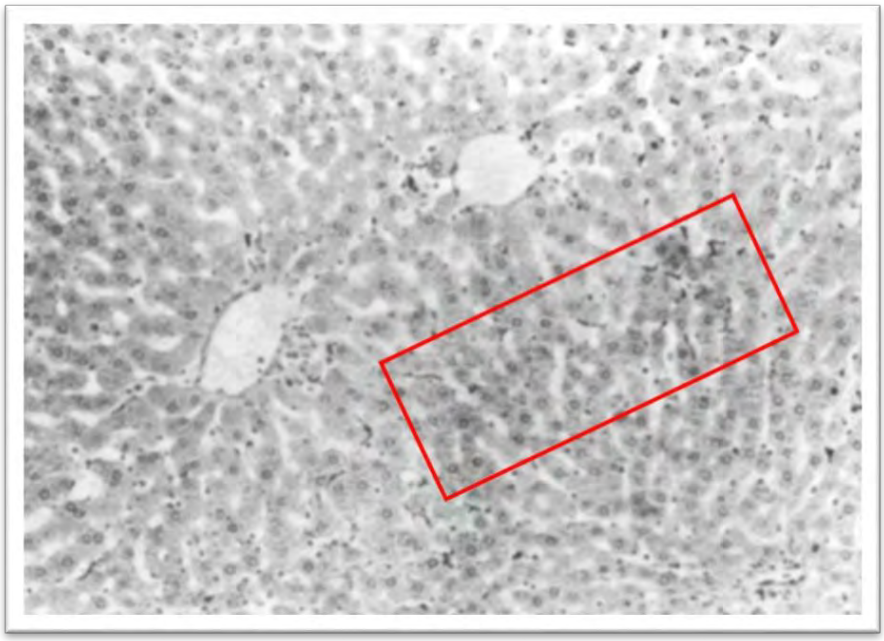


Figure 6. Hypertrophic hepatocytes developed in the central lobular region of the liver obtained at 1 month. H & E; x 160. (Norback and Weltman 1985)

While Bennett's study could not address the issue of cancer because the exposures were insufficiently long, one of his experiments did address the issue of whether the mitotic figures could simply have represented regeneration of damaged cells, indicating repair of the liver.[14] After dosing the rats for approximately 130 days, PCB exposure was discontinued. The livers were then given the opportunity to recover for 2 months (which is normally a sufficient period of time for the liver to show a more normal appearance). The damaged rat livers did *not* recover, which was acknowledged in the following statement regarding for rats exposed to Compounds D and F (90% Compound D with 10% Compound F):

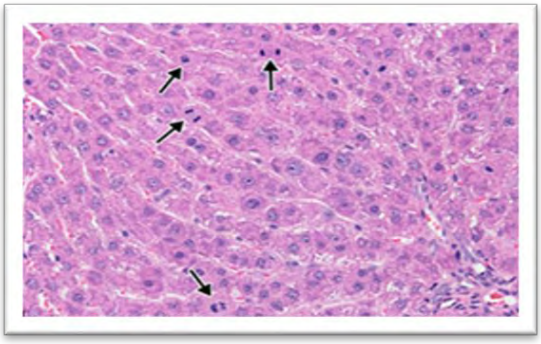
> *These lesions were still demonstrable after a 2 month's recovery period.*

This suggests the tumorigenic progression was not halted.

However, Bennett did observe that cells were rapidly dividing, undergoing extensive cell division. He stated, "mitotic figures were present in abnormally large numbers," which is clear

evidence of hyperplasia, a well-established prerequisite step in tumorigenesis since the basic definition of cancer is uncontrolled cell division. Tumors develop from these hyperplasic cells that are rapidly undergoing rapid mitotic cell division. Cells that are seen at the light microscope level undergoing cell division are dividing in a process known as mitosis (i.e., it is the chromosomes that are made visible with stains under the light microscope). These mitotic cell divisions are called *mitotic figures*. As shown in the photomicrograph of a liver section below, they are easily identified. (Exhibit 9; National Toxicology Program [NTP].[32])

Exhibit 9. National Toxicology Program
Photomicrograph of Mitotic Figures in a Liver Section[32]



Note: Four arrows point to mitotic figures
Source: https://ntp.niehs.nih.gov/nnl/hepatobiliary/liver/hinmitos/index.htm

During organ growth (organogenesis) in early development, mitotic figures are numerous as the cells need to multiply for the organ to grow in size. However, once an organ such as the liver reaches its functioning mature size, the cells no longer divide, except in response to injury or cancer. As stated by the NTP, mitotic figures are rare, except in certain conditions.[32]

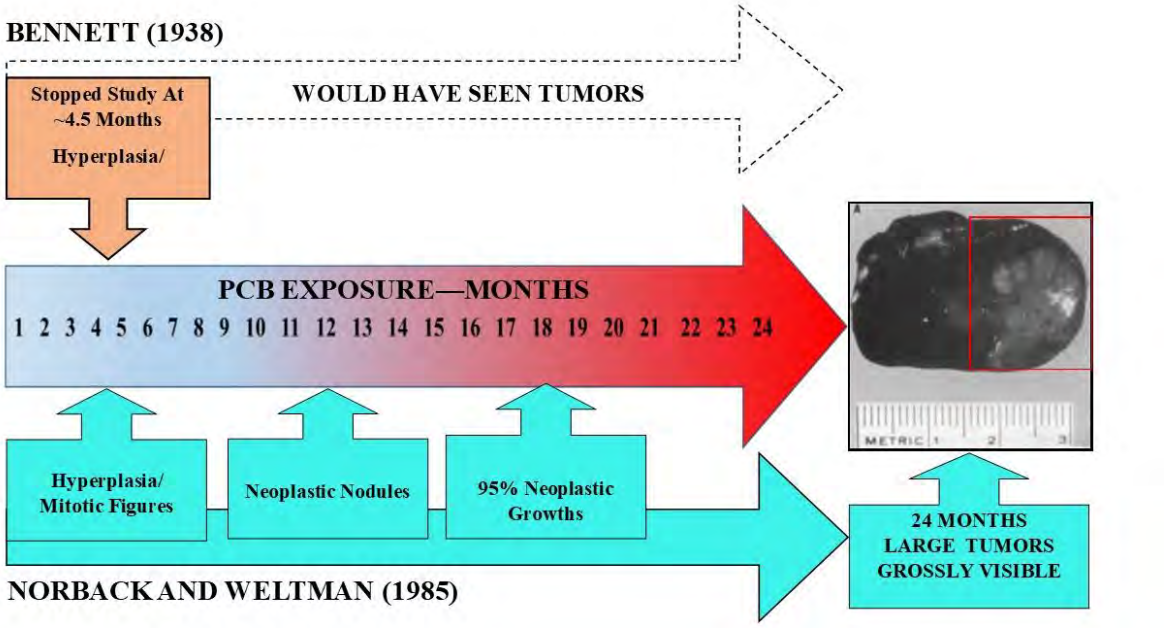
> *A high mitotic frequency can be seen during phases of early growth, during physiologic conditions such as pregnancy, or in rodents bearing tumors at other sites. While occasional mitoses can be seen in a normal liver, finding more than one or two mitoses per 10 high-power fields is not typical for adult rodents. In this example* [photomicrograph shown above]*, the high frequency of mitosis*

> *(arrows) is a repair response following hepatocyte loss secondary to treatment with a hepatotoxicant* [liver toxicant].

The NTP recommends that in toxicity studies where more than a few mitotic figures are produced in response to a toxic chemical, the study should "grade" or score the increase in mitotic figures and report the results. "An increased frequency of mitosis is unusual; it should be documented whenever present and given a qualitative severity grade." There is a limit to how many times a cell can divide (typically, 50–70); under normal circumstances, the cell simply dies once that limit is reached. This occurs through a process known as *programmed cell death* or *apoptosis*. However, in response to chemical carcinogens such as PCBs, the normal process of programmed cell death can be aborted, allowing the cell to become "immortal" (caused by complex carcinogen-induced genetic changes to specific genes in the DNA). This means that the damaged cell can now essentially divide forever forming a tumor mass giving rise to the hyperplasia Bennett[14] described in 1938.

The Bennett studies reported the same early hallmarks of cancer produced by PCB exposure as those described by Norback and Weltman in 1985.[28] But while Bennett terminated his experiment after only 3.5 months, Norback's study was a lifetime PCB cancer study in which the pathological changes were followed over time until the animals were killed at 2 years. I illustrate the comparison by juxtaposing the Bennett findings at 3.5 months to the sequential tumorigenic steps described by Norback in Exhibit 10.

Exhibit 10. Comparison of Bennett[14] Results with Norback and Weltman[28] Results



The most obvious hallmark of cancer is the high proliferation of liver cells in the early stages, which is termed hypoplasia and mitotic cell division. Both Bennett and Norback describe this event occurring during the early months of PCB exposure. Norback shows these early changes progress to tumors.

The focus on mitotic figures is not an esoteric aspect of cancer only used in basic research. Identifying and quantifying mitotic figures in biopsies taken from suspicious growths or palpable tumor masses are fundamental to clinical oncology practice. All pathologists specializing in cancer and oncologists treating cancer patients rely on the *mitotic index* to make important decisions (Ha 2016) regarding cancer patients' treatment and care.[33] The mitotic index is the most widely used metric to: 1) diagnose cancers; 2) stage cancers (determine how far the cancer has progressed); 3) assess a cancer's aggressiveness; and 4) make cancer prognoses. In clinical cancer practices, as well as in all fields of cancer research, the mitotic index is now a basic and routine measurement because it is the most useful and simple method for analysis of cell

proliferation. Determining the mitotic index is a simple matter of counting the number of mitotic figures in tissue specimens within a prespecified area at low magnification.

3.2.6.1. 1939: Mitotic Figures Are Known Early Cancer Hallmarks

Although the mitotic index has been well-established as one of the most important tools in cancer research and clinical practice, and I have conducted extensive historical research into the state-of-the-science at the time, including what was known about mitotic figures and whether they were being interpreted as early indicators of cancer.

I have identified specific studies to highlight what was known at different time points regarding the pathological findings of mitotic figures and whether an objective Monsanto scientist would have identified them as early indications of cancer. Based on my research, I have concluded that a reasonable scientist conducting any toxicological animal experiment investigating pathological damage (in any organ) would have been well aware that mitotic figures were early hallmarks of cancer. The importance of mitotic figures was not only well-established as a toxicological indicator of cancer by the time Drinker published his first study in 1937, but the mitotic index was already widely used both in both general cancer studies and in clinical practice by those diagnosing and treating cancer patients. By 1939, hundreds of studies were clearly relying on the appearance of mitotic figures as the single *key* pathological hallmark for all types of cancers. From the more than 75 published studies and abstracts I reviewed, I have selected several key publications from 1889 to 1939 (when the last of the Drinker studies was published) as supporting evidence that the mitotic figures identified in the Drinker studies should have been interpreted as heralds of developing cancer. By 1939, mitotic figures were routinely used to: 1) identify cancers, 2) diagnose cancers, 3) quantify growth rates of cancers, and 3) make prognoses on likelihood of survival based on the type and aggressiveness of tumors.

In 1965, Triolo provided a well-researched and chronological construction of the history of cancer pathology studies, of which mitotic figures were the key visual identifiers, in his article entitled, “Nineteenth century foundations of cancer research advances in tumor pathology, nomenclature, and theories of oncogenesis.”[34] He traced the first studies that recognized

mitotic figures as important pathological features in cancer, which were published as early as 1889. At this early time point, scientists were observing fully developed tumors in which aberrant mitotic figures were under intense study:

> *The cytology of cancer was given special consideration by the peripatetic pathologist Edwin Klebs (1889) whose theory of cancer formation as a conjugation of epithelial cells and leukocytes largely grew out of the assumption that the neoplastic cell demonstrated a characteristically atypical (asymmetric) mitotic behavior* [emphasis added] *in which fragments of leukocytes participated. (The question of pathologic mitosis already had become a lively research issue…*

Beginning in 1894, Houser published a series of studies advancing his conclusions regarding the cellular changes in skin cancer, of which mitotic "behavior" was a key feature. Triolo wrote:

> *In a series of articles (179-182) Hauser contended that connective tissue alterations were entirely incidental to the performances of the epithelium in the development of carcinoma…According to Hauser, cancerous degeneration was associable with a biologic disordering of the epithelium, in which the cells appeared to undergo a loss of normal physiologic function by virtue of derangements in the cellular and nuclear dimensions, chromatin content, mitotic behavior* [emphasis added]*, and protoplasmic character.*

By the early 1900s, cancer studies were so advanced that elegant studies were being conducted on tumor transplants to evaluate their survival and growth rates when tumors were grafted between species (typically between rats and mice). Mitotic figures were used to not only identify the transplanted cancerous cells but to track their growth rates in the host tissue. For example, Murphy and Nakahara published a study in 1920 that relied on mitotic figures to characterize the appearance of cancer and confirm transplanted tumor cells were indeed growing in the spleen.[35]

> *Spleen -The stimulation of germinal centers was manifest 48 hours after the blood injection. In a section taken at this stage an average nodule usually contained a few well marked mitotic figures* [emphasis added]*, three to five as a rule, more rarely six or seven. All stages of mitosis* [emphasis added] *were easily*

distinguished…The frequency of mitosis [emphasis added] *in the germinal center after 4 days was apparently greater than before (Fig. 1).*

Exhibit 11 presents Figure 1 referred to in the preceding quote from Murphy and Nakahara.

Exhibit 11. Figure 1 from Murphy and Nakahara (1920), Germinal Center of the Spleen with Mitotic Figure[35]

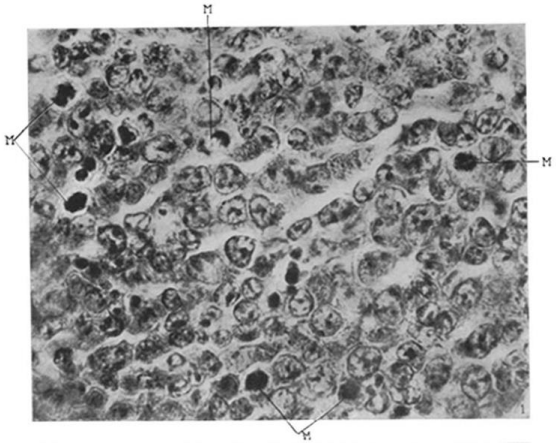


Fig. 1. Germinal center of the spleen 4 days after the blood injection. M, mitotic figure

In 1925, Ludford authored a lengthy treatise on "The general and experimental cytology of cancer."[36] Combining his research with an extensive review of more than 50 published studies, he described key cellular hallmarks of cancer for research and clinical diagnosis purposes. Ludford's extremely detailed descriptions of the appearance (morphology) of cancer cells includes many discussions of mitotic figures. Ludford, published his work more than a *decade* before Drinker's first PCB study was published in 1937. Most notably, he discusses at some length the appearance of mitotic figures as a key feature in developing tumors. Ludford extended his discussion of mitotic figures to identify both normal mitotic figures (that appear in the early cancer stages) to aberrant mitotic figures (that appear in fully formed malignant tumors). His detailed drawings of mitotic figures are no different from those used today by toxicologists in cancer studies to identify different stages of cancer.

One of Ludford's schematic drawings is presented in Exhibit 12, and it is noteworthy that his review is one of the first publications to correct the previous misconception that tumors develop from aberrant mitotic cell division. Ludford correctly concluded that while aberrant mitotic figures are present in tumors, cells with atypical mitoses are aborted and die because they are so damaged and compromised that they cannot undergo further cell division and contribute to the tumor mass. In other words, aberrant mitotic figures have no diagnostic importance. The total number of mitotic figures is the only important feature needed to identify cancerous tissue.

Exhibit 12. Figure 13 from Ludford (1925), Variations in the Mitotic Process in Cancer Cells[36]

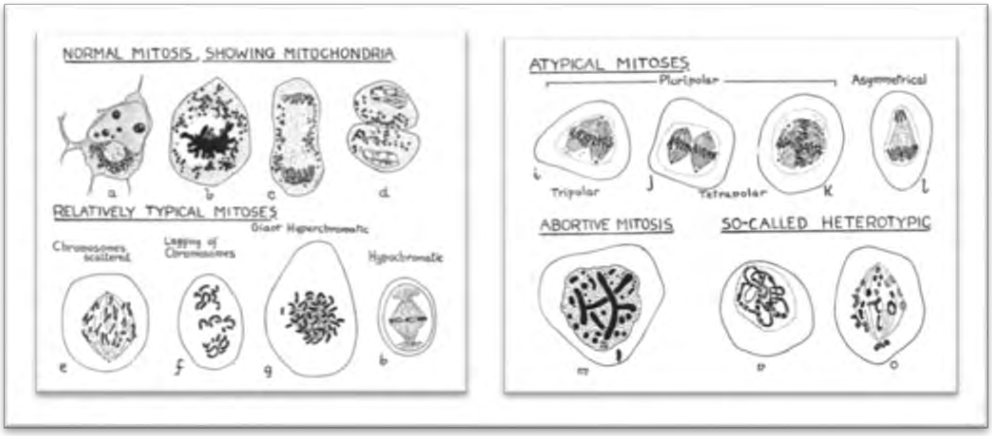


Figure 13. Variations in the mitotic process in cancer cells

On this topic, Ludford concluded that mitotic abnormalities do not contribute to tumor growth and that they are secondary results of tumor growth.

> *The experimental investigation of the conditions favouring* [sic] *abnormal mitosis, together with the observation of cells in tissue cultures, indicate, then, as Ewing says, that the abnormalities are secondary results of tumour* [sic] *growth, and not primary and essential.*

He discussed the frequency of detecting normal and abnormal mitosis with regard to establishing the growth rate of tumorigenesis, which is the key indicator of the aggressiveness of different cancer tumors, as follows:

> *The frequency of occurrence of abnormalities in mitosis is subject to a great deal of variation. Usually in slow-growing tumours* [sic] *there are relatively few mitoses, and these are of the normal type, but with more rapid growth the mitotic figures are more numerous and exhibit abnormalities, especially where degeneration occurs, and where there is a marked inflammatory reaction.*

Ludford noted that the mitotic figures are more numerous when *degeneration* and *inflammation* reactions occur in damaged organs. This is noteworthy because Drinker's findings included both degenerative changes and inflammation in the PCB rat livers. In 1935, Mendelsohn reconfirmed that mitotic figures alone were the only hallmark necessary to identify cancers (abnormal mitotic figures were not important for diagnosis of developing tumors).[37]

> *At the present time asymmetrical divisions are not considered to be diagnostic for malignancy, but their occurrence in malignant tissues is not disputed. Some animal tumors are characterized by many abnormal figures and others by a smaller number, but there is none in which abnormal figures have never been found. Their presence in normal regenerating and inflammatory tissue seems to have been accepted by many investigators. However, a review of the literature will reveal that the occurrence of abnormal mitoses in normal tissues is still a moot question; if they are present they must be rare. Levine (1931) has published a comprehensive review with especial emphasis on mitosis in cancer cells.*

The point that Bennett would not have had to conduct a sophisticated, lengthy, and time-consuming pathological investigation of the complex morphology of mitotic figures, differentiating normal and abnormal mitotic figures. The sole finding of mitotic figures was sufficient to cause concern that PCBs were carcinogenic.

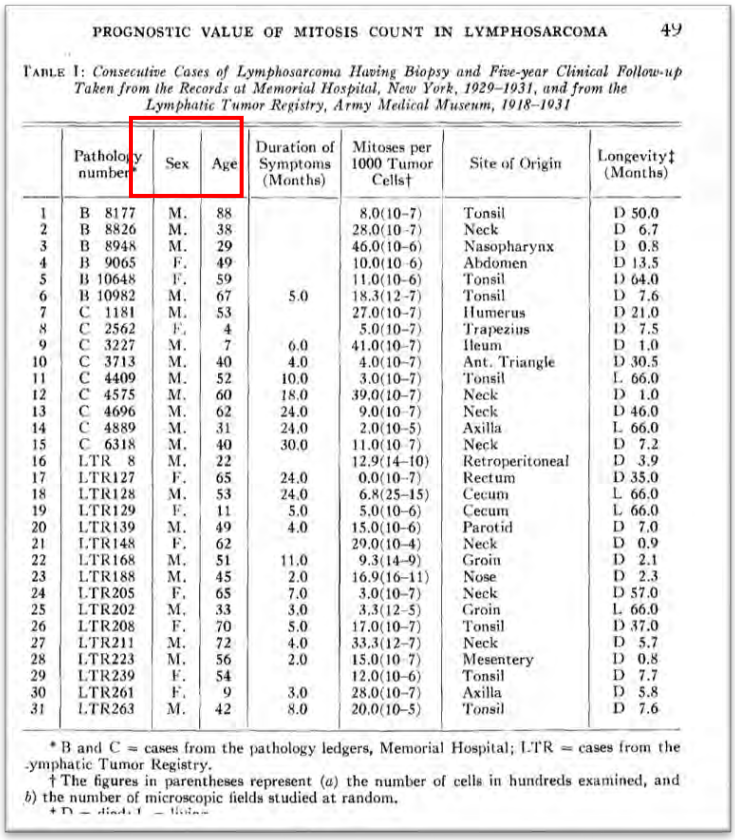
By 1937, counting the number of mitotic figures was so established and routine that clinical pathologists were relying on this diagnostic feature as the sole cancer hallmark to estimate survival rates from tumorous growths. For example, in the same year Bennett published his first

study (1938), Casey published a study investigating the prognostic value of using the mitotic index to evaluate both the longevity and mortality associated with lymphosarcoma tumors (lymphosarcomas are among the group of non-Hodgkin lymphomas that IARC has linked to PCB exposures).[38] In his introduction, Casey noted that the mitotic counts for the primary tumor, metastases (secondary tumor that has traveled to another organ), and recurrent tumors had the same mitotic index as biopsy tissue. Using the mitotic index had now become such a standard and routine pathological practice in 1937 that Casey was able to rely solely on this single criterion to differentiate between malignant and benign tumors. Furthermore, he concluded mitotic counts in animal tumors were similar to those in human tumors:

> *The evidence obtained indicated that the primary tumor, the metastases, and the recurrences had the same mitotic coefficient* [emphasis added] *in biopsy material. Autopsy specimens have not been studied sufficiently. Tumors of man have been found to have mitosis counts* [emphasis added] *similar to the tumors of other mammals. Malignant tumors have shown more than 4 mitoses per 1000 tumor cells and benign tumors less than 4 mitoses per 1000 tumor cells, irrespective of type, site, and mammalian species.*

Casey's results of the mitotic counts (column in red rectangle) in various tumor biopsy specimens versus patient longevity are presented in 0.

Exhibit 13. Table I from Casey (1937), Prognostic Value of Mitosis Count in Lymphosarcoma[38]



PROGNOSTIC VALUE OF MITOSIS COUNT IN LYMPHOSARCOMA 49

TABLE I: *Consecutive Cases of Lymphosarcoma Having Biopsy and Five-year Clinical Follow-up Taken from the Records at Memorial Hospital, New York, 1929–1931, and from the Lymphatic Tumor Registry, Army Medical Museum, 1918–1931*

	Pathology number*	Sex	Age	Duration of Symptoms (Months)	Mitoses per 1000 Tumor Cells†	Site of Origin	Longevity‡ (Months)
1	B 8177	M.	88		8.0(10–7)	Tonsil	D 50.0
2	B 8826	M.	38		28.0(10–7)	Neck	D 6.7
3	B 8948	M.	29		46.0(10–6)	Nasopharynx	D 0.8
4	B 9065	F.	49		10.0(10–6)	Abdomen	D 13.5
5	B 10648	F.	59		11.0(10–6)	Tonsil	D 64.0
6	B 10982	M.	67	5.0	18.3(12–7)	Tonsil	D 7.6
7	C 1181	M.	53		27.0(10–7)	Humerus	D 21.0
8	C 2562	F.	4		5.0(10–7)	Trapezius	D 7.5
9	C 3227	M.	7	6.0	41.0(10–7)	Ileum	D 1.0
10	C 3713	M.	40	4.0	4.0(10–7)	Ant. Triangle	D 30.5
11	C 4409	M.	52	10.0	3.0(10–7)	Tonsil	L 66.0
12	C 4575	M.	60	18.0	39.0(10–7)	Neck	D 1.0
13	C 4696	M.	62	24.0	9.0(10–7)	Neck	D 46.0
14	C 4889	M.	31	24.0	2.0(10–5)	Axilla	L 66.0
15	C 6318	M.	40	30.0	11.0(10–7)	Neck	D 7.2
16	LTR 8	M.	22		12.9(14–10)	Retroperitoneal	D 3.9
17	LTR127	F.	65	24.0	0.0(10–7)	Rectum	D 35.0
18	LTR128	M.	53	24.0	6.8(25–15)	Cecum	L 66.0
19	LTR129	F.	11	5.0	5.0(10–6)	Cecum	L 66.0
20	LTR139	M.	49	4.0	15.0(10–6)	Parotid	D 7.0
21	LTR148	F.	62		29.0(10–4)	Neck	D 0.9
22	LTR168	M.	51	11.0	9.3(14–9)	Groin	D 2.1
23	LTR188	M.	45	2.0	16.9(16–11)	Nose	D 2.3
24	LTR205	F.	65	7.0	3.0(10–7)	Neck	D 57.0
25	LTR202	M.	33	3.0	3.3(12–5)	Groin	L 66.0
26	LTR208	F.	70	5.0	17.0(10–7)	Tonsil	D 37.0
27	LTR211	M.	72	4.0	33.3(12–7)	Neck	D 5.7
28	LTR223	M.	56	2.0	15.0(10–7)	Mesentery	D 0.8
29	LTR239	F.	54		12.0(10–6)	Tonsil	D 7.7
30	LTR261	F.	9	3.0	28.0(10–7)	Axilla	D 5.8
31	LTR263	M.	42	8.0	20.0(10–5)	Tonsil	D 7.6

* B and C = cases from the pathology ledgers, Memorial Hospital; LTR = cases from the Lymphatic Tumor Registry.

† The figures in parentheses represent (*a*) the number of cells in hundreds examined, and (*b*) the number of microscopic fields studied at random.

‡ D = died; L = living.

Finally, Casey concluded the following:[38]

> *A high and significant correlation was found between the mitosis count in biopsies of lymphosarcoma and the longevity and mortality from the tumors after biopsy. The study was objective in that the diagnosis was made by others and the clinical outcome was not known to the author at the time the mitosis count was made.*

This conclusion was based on the results of mitotic coefficients versus mortality at different survival times, as show in Exhibit 14:

Exhibit 14. Table III from Casey (1937), Mortality from Lymphosarcoma for Various Mitotic Coefficients[38]

TABLE III: *Mortality from Lymphosarcoma for Various Mitotic Coefficients*

Mitoses per 1000 Tumor Cells	Interval	Cases	Mortality at One Month after Biopsy	Mortality at Six Months after Biopsy	Mortality at Twelve Months after Biopsy	Mortality at Three Years after Biopsy	Mortality at Six Years after Biopsy
0–3	4	5	0%	0%	0%	20%	40%
4–11	8	10	0%	10%	30%	50%	80%
12–27	16	9	11%	33%	77%	100%	100%
28–59	32	7	57%	100%	100%	100%	100%

In addition to these cancer studies and use of the mitotic index in all areas of oncology and clinical pathology, mitotic figures were the key morphological feature of studies on *chemically induced* cancers. By 1939, many studies had been published in which counting mitotic figures allowed scientists to detect the early stages of cancer and follow tumor development induced by *chemical carcinogens*. For example, Morton et al. (1936) investigated benzene-based chemicals triphenylbenzene and tetraphenylmethane isolated from coal tar, and showed they were carcinogenic in animal studies.[39] They described the tumor mass as follows:

> *The cells show variations in size, shape, and staining reaction, the cytoplasm being rather uniformly strongly acidophilic, while the nuclei tend to be large, clear and vesicular, and show considerable variation in size and shape. Numerous irregular mitotic figures* [emphasis added] *are encountered and not infrequently very large cells are noted… Cells comprising this infiltrating mass tend to be rather large, clear and vesicular in character, the nuclei being particularly irregular in size and shape. Mitotic figures* [emphasis added] *are encountered.*

Barnes and Furth (1937) conducted cancer investigations in laboratory animals by exposing them to benzpyrene (a benzene-based compound), another carcinogen isolated from coal tar.[40] When injected into the spleen, benzpyrene caused cancer of the blood cells. When these

malignant cancer cells circulated in the bloodstream, they lodged in the liver, where they were identified based on their mitotic count. In other words, Barnes and Furth followed the path of cancer cells created in the spleen and transported to other organs using only mitotic counts to identify the malignant blood cells (emphasis added):

> *The liver showed moderate diffuse and perivascular infiltration similar to that shown in Fig. 20. The malignant cells occurred singly or in groups of from four to fifteen scattered throughout the sinusoids. Mitotic figures were numerous* [emphasis added]*...Microscopically the subcutaneous tumor was composed of the atypical cells already described. Mitotic figures* [emphasis added] *occurred in vast numbers, so that as many as nine were found in one field viewed at 900 X magnification.*

In 1939, Brues et al. designed a clever experiment to investigate the "cancer potency" between similar carcinogens to determine the precise molecular chemical structure that made one carcinogen more potent than a slightly different carcinogen.[41] This was an investigation delving into the possibility that the *potency* of chemical carcinogens was somehow linked to the latency between the beginning of exposure and when the tumor first appeared. The researchers postulated that more potent chemical carcinogens would have a shorter latency period than did weaker carcinogens. As in previous carcinogen studies, they used the mitotic index to identify developing tumors caused by carcinogens with slightly different chemical structures:

> *Most mice were killed after tumors had reached considerable size and paraffin sections were made. Mitoses were enumerated in groups of 1000* [emphasis added] *or more counted tumor cells…In the 3 groups in which mitosis counts* [emphasis added] *were done, they were seen to show a good degree of correlation with growth rate. Here, again, it was not possible to demonstrate such correlations in individual instances, but only by groups.*

Brues et al. found a correlation between the potency of the different chemical carcinogens and the latency period, summarizing:

> *There is a high degree of correlation between the malignancy of chemically induced tumors, as measured by growth rate and mitotic index* [emphasis added]*, and shortness of the latent period before appearance of palpable tumors. This*

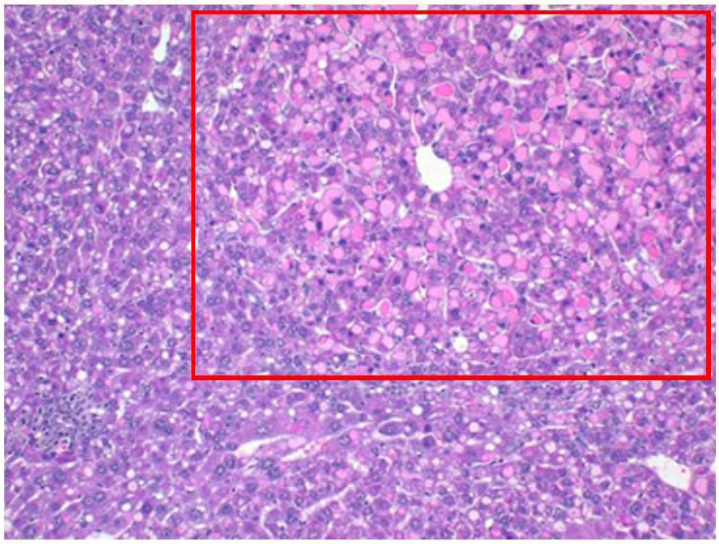
> *relation holds true in the various responses of different strains of mice to the same agent, and in responses to different agents and modes of administration.*

In summary, the historical studies previously described clearly show that the general state-of-the science regarding the importance and significance of mitotic figures as early hallmarks of cancer was well established a decade before the Bennett studies were published. Many toxicity studies published in the 1930s considered mitotic figures to be the most obvious and key pathological feature of cancer.

3.2.7. 1939: Mitotic Figures Were Cancer Hallmarks

In addition to mitotic figures, the other pathological hallmark of cancer emphasized by Bennett was *hyaline bodies*. Scientists studying these structures in cancerous tissue also referred to them as *hyaline inclusions* or *droplets*. A microphotograph produced by the National Institute of Environmental Health Sciences (NIEHS) as part of its Digitized Atlas of Mouse Liver Lesions shows hyaline bodies, which are readily identified in this image as numerous light pink-staining liver cells (Exhibit 15).[42]

Exhibit 15. National Institute of Environmental Health Sciences Photomicrograph of Hyaline Bodies[42]



Source: https://www.niehs.nih.gov/research/resources/visual-guides/liverpath/degenerative/hyaline_bodies/index.cfm

NIEHS describes hyaline bodies as being seen in liver degeneration, as well as in hepatocellular neoplasms. Despite Bennett's reporting that hyaline bodies are characteristic of the pathological changes that occur with PCB exposures,[14] Monsanto's scientists conducted no follow-up studies to determine the eventual outcome of these damaged cells. That is, since hyaline bodies can be evidence of degeneration or developing cancers, Monsanto should have confirmed whether the livers would develop tumors. It is now well-known that PCB exposure is associated with developing hyaline bodies and that cancer does indeed develop with prolonged PCB exposure.

These bodies have more recently been studied to determine the composition of the hyaline material that builds up in cancerous liver cells. In 1999, Stumptner et al. published a detailed study of these structures, describing both the morphology and composition of these malignant structures.[43]

> *HCC cells* [hepatocellular carcinoma cells; liver cancer cells] *may contain a variety of intracytoplasmic inclusions differing in morphology and chemical composition.…However, IHBs*…[intracytoplasmic hyaline bodies] *so far evaded further characterization. The HCC case presented in this communication was exceptional as IHBs were particularly numerous in the tumor cells allowing further analysis of this material.*

It is my opinion that, like mitotic figures, hyaline bodies were well-established as morphological indicators of liver cancer at the time Bennett published his studies. To support this opinion, I conducted a similar historical literature review to establish a timeline showing when these hallmark cancer structures were first identified in tumor cells, when it became common or general knowledge, and when they were routinely used as visual indicators to identify liver cancers. The following sections highlight just a few of the numerous published studies that were published well before the Bennett studies were completed.

In the previously described 1965 Triolo review in which he detailed the use of mitotic figures for identifying cancerous tissues,[34] Triolo stated that hyaline bodies were first reported by Muller as early as 1836 as being a specific and morphologically distinct category of cancer.

> *Muller's results, a part of which were reported as early as 1836…prompted him to reject the Laennecean concept of heterologous tissues and to adopt a cellular basis for tumor taxonomy. He distinguished according to cell type, (a) fibrous or scirrhus cancer, (b) reticular cancer, (c) alveolar or colloid cancer, and (e) hyaline cancer.* [Emphasis added.]

One of the first published studies that referred to hyaline bodies in cancer was "An address on characteristic organism of cancer" by Russell in 1890.[44] He reviewed numerous studies and reported the following:

> *"Professor Klebs published, in June of this year…papers "On the Nature and Diagnosis of Cancer Formation," in which he discusses these questions with fairness and masterliness* [sic]. *In them he refers to hyaline bodies* [emphasis added] *present in cancer, which, however, he is decidedly disposed to regard as degenerative products… I am, however, disposed to regard most of his hyaline bodies* [emphasis added] *as productions of the cells, for hyaline masses* [emphasis

> added] *are frequently present, and are easy of recognition* [emphasis added] *in the alveoli of the more adenomatous cancers…*

Hyaline bodies were some of the most obvious hallmarks used in clinical practice to identify tumors in biopsy tissue or excised livers tumors. For example, Keen (1899) reported his findings of a liver tumor mass he removed from a patient that had the following appearance:[45]

> *Immediately adjacent to this wall begins the extensive necrotic change which permeates the whole tumor. It would seem that fully 80 per cent. of the tumor mass, if not more, is made up of cellular detritus, caseous, or hyaline material.* [Emphasis added.]

By 1925, it was well-established that malignant cancers develop in tandem with degenerative changes for some chemical carcinogens. That is, while some chemical carcinogens only produce cancerous tumors (with only slight evidence of cell damage), some carcinogens produce both severe *degenerative* changes that occur in tandem with malignant cell growth that eventually lead to tumor formation. PCBs fall into the latter category. Ludford stated that while investigating tumors, areas of degeneration are common.[36]

> *Since areas of necrosis [cell degeneration] are of common occurrence in tumours, all stages of cellular degeneration are seen in histological sections.*

In tumors, cells undergoing degeneration form intracellular hyaline bodies and become one of the distinguishing features of the tumors themselves. They are easily visible with common stains used in the laboratory (as shown in Exhibit 15 with the pink-stained cells):

> *Retrogressive changes in the ground cytoplasm often result in the formation of granules of different kinds, and hyaline droplets.* [Emphasis added.] *Some of these products of cytoplasmic degeneration exhibit special affinities for stains. Hyaline droplets* [emphasis added] *stain specially with fuchsin, and were at one time regarded as cancer parasites.*

Ludford stated that hyaline bodies by themselves may not be specific to cancer but that since degeneration occurs in tumors, they are one characteristic that can be used to follow developing tumors.

Hyaline bodies were characteristic clinical diagnostic indicators of tumors produced by chemical carcinogens. Twort and Twort (1935) conducted a series of experiments to evaluate whether carcinogens would produce tumors when directly applied to organs.[46] They explained their investigations in which they applied carcinogens to the surfaces of different organs. They then evaluated those organs for the presences of cancer hallmarks or "special features," including hyaline bodies. They stated:

> *The organs with which we shall deal are the skin, liver, spleen, thyroid, parathyroids, brain, and pituitary gland. The special features relating to the organs with which we are at the moment concerned are…*
>
> > *Liver: Presence of fatty infiltration (condition X) and hyaline degeneration.* [Emphasis added.]
> >
> > *Spleen: Size of organ and presence of hyaline degeneration.* [Emphasis added.]
> >
> > *Thyroid: Size of organ, presence of hyaline degeneration* [emphasis added]*, colloid and parathyroid.*

Twort and Twort used different benzene-containing synthetic hydrocarbon carcinogens to produce skin cancer. The diagnostic feature used to identify malignant skin cancer tumors was hyaline bodies, as shown in their table, which is presented in 0.

Exhibit 16. Table 11 from Twort and Twort (1935), Effect of Three Hydrocarbons on the Spleen[46]

TABLE 11: *Effect of Three Hydrocarbons on the Spleen*

Agent	No.	Per cent Large	Per cent with Hyaline Degeneration
H. C. 7	378	20	19
H. C. 8	162	42	54
H. C. 9	51	59	69

I continue this discussion of hyaline bodies as hallmarks of cancer in my discussion of the Miller (1944) PCB study in section 3.3 below.[17]

In summary, mitotic figures and hyaline bodies were used as primary indicators of the early stages of cancer and to follow the progression of tumorigenesis well before the Bennett study was published.

Even if Monsanto's toxicologists did conclude, after reviewing Bennett's findings, that they only represented degenerative liver damage, the fact that the severe and extensive degenerative pathological lesions were still present in animals that were allowed to recover for 2 months after PCB exposure was stopped should, by itself, have triggered further studies. If longer exposure studies had been performed ostensibly only for the purpose of following the progression and outcome of the "degenerative" lesions, Monsanto's scientists would have found tumors in the livers, even if the intended purpose of the study was not to identify PCB-induced tumors.

3.3. 1944: Dr. Miller

Miller J.W. Pathologic changes in animals exposed to a commercial chlorinated diphenyl. Public Health Reports. 1944; 59(33):1085–1093.[17]

Like the Bennett study,[14] the 1944 Miller PCB exposure study[17] should have been another trigger for Monsanto to have conducted long-term animal cancer studies.

By 1939, when the last of the three Drinker studies was published,[24] there was no uncertainty that PCBs caused severe and long-lasting systemic liver damage and initiated the early steps in tumorigenesis. However, because the Bennett studies were essentially *cause of death* applied toxicity studies, there were several fundamental and basic toxicity questions that needed to be addressed. For example, the Bennett studies only focused on the liver because the Halowax workers died of liver disease, but could PCBs also produce toxic effects in other organs? Since the Bennett studies only investigated the effects in the liver, their results could not be used to answer questions about toxicity/cancer in other organs.

The Bennett studies only used rats, so it was also not known whether rats were the most sensitive or were representative of human toxicity (most well-designed basic toxicity studies use multiple test species). To address outstanding questions, the US Public Health Service conducted a series of very robust toxicology studies that confirmed and extended the Bennett's results regarding PCB toxicity. If Monsanto's toxicologists had any outstanding questions after carefully reviewing the Drinker studies, they could not claim as much after reviewing the Miller study in 1944.

The Miller study was published not in an obscure or rarely read scientific journal, but rather in a National Institutes of Health, Public Health Report, based on research conducted in the Industrial Hygiene Research Laboratories—a highly regarded publication by industrial hygienists in all fields of chemical manufacturing operations.

In 1944, Dr. Miller, who was a Surgeon with the United States Public Health Service (US PHS; founded in 1798, it is the oldest governmental health agency), published the results of numerous toxicity studies that were conducted with a commercial Aroclor (Aroclor 1242). As a doctor employed in the US PHS, Dr. Miller's professional responsibility as a US PHS officer was to monitor and identify potential health threats posed by industrial chemicals to the general public and workers. That is, he was responding to empirical work-related evidence that PCBs were already causing health-related problems and could represent an emerging health threat to workers and the public.

While Dr. Miller published the Aroclor study, the experiments were actually conducted in the US National Institutes of Health, Industrial Hygiene Research Laboratories, by Surgeon B.J. Jones and Physiologist D.D. Donahue. Miller's study significantly extended the Drinker findings for the following reasons:

1. Animals were exposed to a pure commercial biphenyl: Aroclor 1242;
2. Multiple animal species were exposed to the Aroclor (rats, mice, and guinea pigs);
3. Animals were exposed via multiple exposure routes;
4. All major organs were examined for pathological damage; and
5. It provides direct evidence that PCB-induced pathology included the early hallmarks of cancer, not only in the liver but in the immune system (Drinker did not investigate any changes related to blood cancers).

While the Miller study investigated PCB-induced damage in all organs, the pathological lesions reported specifically for the liver were nearly identical to Bennett's description of the lesions. This supports my conclusions regarding the severe damage produced by formulations that included PCBs, as discussed for the Bennett studies.

Dr. Miller was very clear in clarifying the purpose of his study:

> *The demands of industry as a result of the war have greatly increased the use of chlorinated naphthalenes and chlorinated diphenyls. In the past few years the hazards associated with their application have attracted much interest and a number of reports regarding the systemic and dermatologic effects of exposure, including fatal cases, have been made.*

He also emphasizes that his study would only focus on Aroclor 1242 (to avoid any confusion regarding the interpretation of his toxicological results):

> *Only the pathologic changes in animals exposed to a commercial chlorinated diphenyl* [Aroclor 1242] *are given here.*

Miller noted that there was a consistent pattern of damage among the different species he tested and that it always involved the liver:

> *Two conspicuous pathologic findings were observed-liver damage in all series of experiments and skin changes in the animals receiving subcutaneous injections or applications of the material to the skin.*

Interestingly, he identified a different sensitivity between toxic responses to PCBs among guinea pigs, rabbits, and rats:

> *It was possible to detect a difference in response of the three species to the material on the basis of liver damage. Most liver damage was found in the guinea pig, less in the rabbit, and least in the rat. This same species order was followed, regardless of dose, duration of test, or mode of administration.*

The importance of this finding is that is not clear what species best represents humans. If guinea pigs are the best representatives of the human toxic response, Bennett's studies likely *underestimated* the PCB toxicity since the Bennett studies only used rats.

Miller cites the previous Drinker studies and concludes the specific PCB-induced pathological changes in the liver first reported by the Bennett study,[14] in which the pathology was reported for a *mixture* of chlorinated diphenyls [PCBs] and naphthalenes), were nearly identical to the pathological lesions he found on exposing rats to pure Aroclor 1242. As did Bennett, Miller identified hyaline bodies as one of the major *unique* PCB-induced pathological lesions in the liver, stating:[17]

> *Intracellular hyaline bodies were found in the liver of the rat alone…They occurred in from 20 to 38 percent of the animals treated in the various ways. They were somewhat less marked in degree and in number of animals when the chlorinated diphenyl was ingested. These findings agree with Bennett who reported similar hyaline bodies in liver cells of white rats exposed to mixtures of chlornaphthalenes and chlorinated diphenyl, chlorinated diphenyl, and less frequently to mixtures of chlornaphthalenes. To date such bodies have only been observed in rats exposed to such chlorinated compounds.* [Emphasis added.]

Miller went on to discuss the importance, appearance, and interpretation of PCB-induced hyaline bodies with regard to the hallmarks of cancer:

> *The hyaline bodies are morphologically different from those produced by butter yellow in hepatic tumor cells. They probably represent further development of the same general type of hyaline degeneration as has been observed with certain azobenzenes.*

This is a very important statement because it compared the appearance of pathological hyaline bodies to known animal and human carcinogens, which were the azo-dyes. It was well known throughout the scientific community by 1944 that azobenzene compounds were used as dyes and cause cancer. In fact, the very first long-term animal study investigating chemical carcinogenesis was conducted more than a decade earlier on azobenzenes—namely, o-aminoazotoluene. In this groundbreaking study by Yoshida in 1932,[47] who is credited with performing the seminal lifetime cancer study in laboratory animals, he dosed animals with azo dyes.

This single study heralded an explosion of cancer studies in the 1930s and 1940s investigating chemical carcinogens. This was noted by Orr and Stickland (1941):[48]

> *"The production of liver tumours* [sic] *in rats by the inclusion of azo-dyes in their diet was first demonstrated by Yoshida [1932; Sasaki & Yoshida, 1935]. In this work the dye used was o-aminoazotoluene (2:1:1:4:3-tolueneazoaminotoluene).*

If Monsanto scientists were not convinced that hyaline bodies were important triggers for cancer after reviewing the Bennett study, the suggestion that PCBs caused pathological lesions similar to azo compounds, which were known animal *and* human carcinogens, should have convinced Monsanto that cancer studies were certainly necessary to address this new finding by Miller.

It is clear that Miller considered hyaline bodies to be the most important pathological lesions produced by PCB in the livers of rats because the only photomicrograph he included in his work is a group of hyaline bodies. It is common practice for scientists to include photomicrographs only for the most important features of a study. While Miller reported many pathological lesions, he only showed the one lesion he thought important. That photo is shown below in Exhibit 17.

Exhibit 17. Plate I from Miller (1944), Intracellular Hyalin Bodies in Livers of rats Exposed to a Chlorinated Diphenyl[17]

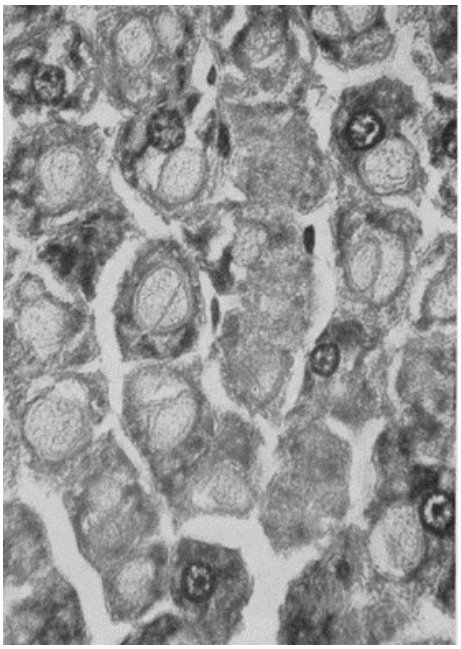


Plate I. Figure 1. Intracellular hyaline bodies in livers of rats exposed to a chlorinated diphenyl.

Another important aspect of Miller's work is that he reported the pathology for three species, exposing the animals through numerous routes of administration. The pathology was "conspicuous" and consistent. He summarized as follows:

> *Guinea pigs, rats, and rabbits were exposed to a commercial chlorinated diphenyl by subcutaneous injections and applications to the skin. The material was also administered to guinea pigs and rats by ingestion and to rats alone by corneal instillations. The doses varied from 17 to 1,380 mg. and were either single or were repeated at regular intervals.*
>
> *Two conspicuous pathologic findings were observed-liver damage in all series of experiments and skin changes in the animals receiving subcutaneous injections or applications of the material to the skin.*

> *Fatty degeneration and atrophy of the centrolobular cells were present in varying amounts and in varying numbers of animals the different test groups. In the rat an additional finding, hyaline bodies within the liver cells, was noted in certain animals.*

Miller also specifically highlighted the fact that the pathological changes were unique to PCBs and emphasized the species difference in sensitivity:

> *Attention is called to the fact that the chlorinated diphenyl used in the above experiments produces liver changes in the rat having marked differences from those resulting from other toxic substances and that such changes were not found in the guinea pig and rabbit… It was possible to detect a difference in response of the three species to the material on the basis of liver damage. Most liver damage was found in the guinea pig, less in the rabbit, and least in the rat.*

Finally, Miller also for the first time identified evidence of cancer not yet reported by Bennett. Miller reported PCB-induced early evidence of lymphomas in the guinea pig, stating:

> *Changes in the spleen were essentially the same except that lymphoid hyperplasia was more frequent and few to moderate numbers of hemosiderin-bearing cells were seen in 12 of 23 animals.*

Which was also seen in rabbits:

> *The changes noted were slight to marked congestion of the cavernous veins and slight to moderate follicular lymphoid hyperplasia.*

If, for any reason, Monsanto was confused or unconvinced about the import of studies conducted prior to Miller's work, his conclusions left no room for uncertainty. Monsanto should have conducted chronic exposure studies to investigate the effects of long-term exposure to PCBs.

4. MONSANTO'S PCB STUDIES FAIL TO ACCOUNT FOR CHRONIC EXPOSURE

Monsanto used contract laboratories to conduct PCB studies from 1934 to 1972. However, not one of these studies was conducted according to the generally accepted standards in the field of toxicology that could be used to derive safe exposure levels to protect the general public. Furthermore, the chronic animal testing Monsanto conducted after 1970 is not credible.

I conclude that Monsanto produced scant relevant, applicable, or credible toxicity information in any of its studies. With very few exceptions, Monsanto did not share any toxicity information with the general scientific community, nor was it peer reviewed or published in any scientific journals.

4.1. With few exceptions, most well-designed, long-term PCB cancer studies have shown strong evidence of cancer.

The protocols used in cancer studies by the mid-1940s were standardized and did incorporate the important features necessary to identify chemical carcinogens, as is evidenced by the fact they did detect cancer. The results and conclusions of the pre-1970 cancer studies have withstood the test of time, and chemicals identified as carcinogens in the 1930s are still considered carcinogens today.[11], [12] Had Monsanto conducted cancer tests for PCBs at that time, the tests would have shown what later tests made clear–that PCBs are carcinogens.

With few exceptions, most well-designed, long-term PCB cancer studies have shown *strong* evidence of cancer as I showed in the EPA Exhibit 5 and Exhibit 6. The evidence of carcinogenicity was so strong in these studies published by independent scientists that it was persuasive to non-toxicologists serving in Congress. It was Congress that banned PCBs in 1976 and not based on EPA scientist's recommendations. For example, a 1976 EPA press release stating why PCBs were being banned, states specifically noted they *caused cancer in animals* (https://archive.epa.gov/epa/aboutepa/epa-bans-pcb-manufacture-phases-out-uses.html):[49]

> *PCBs have caused birth defects and cancer in laboratory animals, and they are a suspected cause of cancer and adverse skin and liver effects in humans. EPA estimates that 150 million pounds of PCBs are dispersed throughout the environment, including air and water supplies; an additional 290 million pounds are located in landfills in this country.*

It is important to note that EPA does not state that PCBs are "suspected" animal carcinogens, but they "caused" cancer in laboratory animals.

I carefully reviewed Monsanto's own cancer study protocols that were developed by IBT and were used to test the carcinogenicity of different Aroclors—there is *nothing* new in its study design that could have not been used by the mid-1940s. Indeed, the same study design used in the later Monsanto studies could have been used by Monsanto in the 1930s, 1940s, 1950s, or 1960s. It is my opinion that *if* Monsanto did conduct lifetime animal cancer studies on each of its Aroclor products (namely, Aroclors 1242, 1016, 1248, 1254, and 1260), those studies would have shown that PCBs were carcinogenic in animals. Most of the studies that were conducted in the 1970s and 1980s, which EPA summarizes in its tables, were positive and show PCBs were animal carcinogens. These studies could have been carried out in the mid-1940s and they would have shown that PCBs were carcinogenic. There is no compelling reason to believe that if those studies were performed prior to the 1970s and 1980s the results would have been significantly different.

I should also stress again, that in evaluating different cancer studies, positive cancer studies carry much more weight than negative studies, for the simple reason that it is easy to conduct a so-called *bad* cancer study that does not show cancer, but it is nearly impossible to force tumors to develop for a chemical that is not a carcinogen. Moreover, negative cancer results are never evaluated separately from positive cancer studies. For example, there are people who are chain smokers and who will smoke until they die but will not develop lung cancer. This negative finding cannot be interpreted to mean that the carcinogens in cigarette smoking do not cause lung cancer.

4.2. It is not the number of PCB studies but the type of studies that determine toxicity and carcinogenicity.

Monsanto conducted only 165 laboratory studies on numerous compounds Monsanto was developing or manufacturing. None of the studies on PCBs can be considered *toxicity studies*; rather, they were lethality studies.

Monsanto conducted only 79 studies on pure biphenyl Aroclor and these studies were crude LD50 studies--not toxicity studies. In fact, there was *zero* data in any of the 79 studies that could be used to derive an acceptable safe chronic exposure level for either workers or the general public (with the exception of the Drinker[24] study that proposed workplace air levels, but that study may not be applicable because it was a subchronic study and they evaluated a mixture of chlorinated compounds). I am aware of no Aroclor study that was relevant to actual anticipated human exposures.

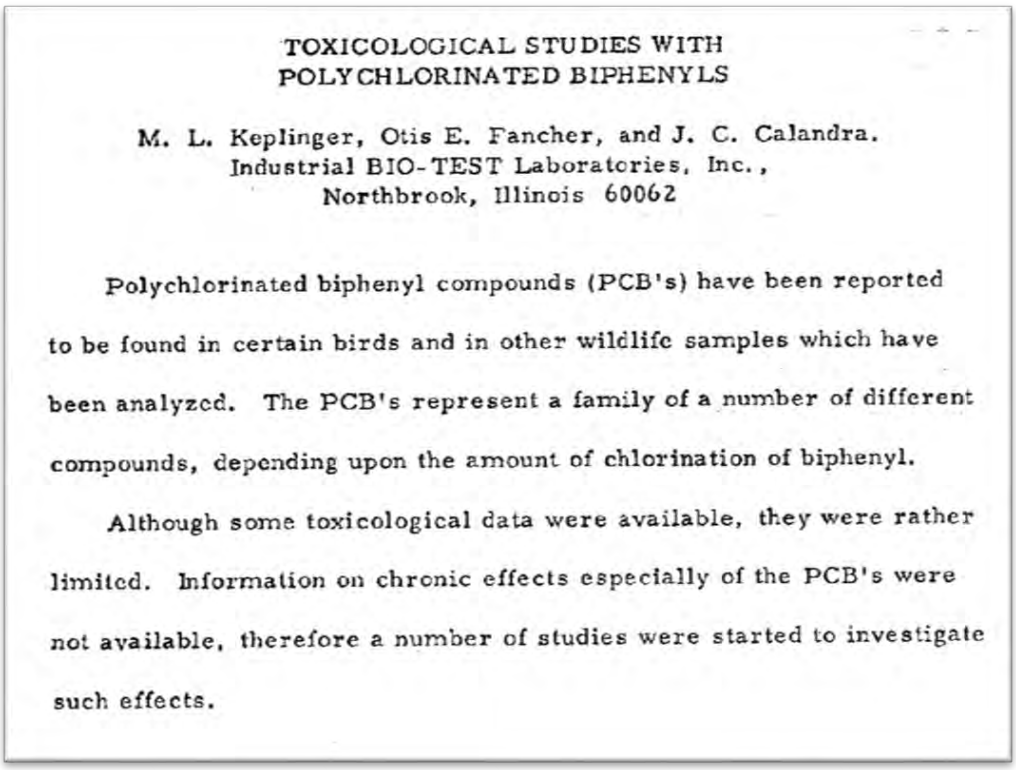
The remaining Monsanto studies are toxicity studies on complex Monsanto mixtures that contained different amounts of PCBs along with other toxic compounds. For example, Pydraul contains organophosphate esters and PCBs. When animals were exposed to Pydraul it is not possible to extract the specific toxic effects contributed by PCBs or organophosphate esters from the overall toxic effect observed in the study. The Pydraul toxicity studies are relevant to sites where Pydraul exposures have occurred, but not to sites where Aroclor exposures are the focus. This being said, even if the confounding influence of the complex mixtures could somehow be untangled, these remaining studies would still be unusable for evaluate the chronic exposures associated with PCB either in the workplace or for the general public.

In summary, Monsanto conducted *no* credible toxicology study that is relevant and useful for determining the systemic toxicity from chronic exposures prior to 1970.

4.3. The studies commissioned by Monsanto in the 1930s through the 1960s were not applicable to the evaluation of human toxicity for Monsanto's workers or the general public.

Monsanto generated little toxicology information and what they did generate was largely unusable. The president and principal scientists of Monsanto's own toxicology contract laboratory's statements support my opinion. Prior to 1966, Monsanto had consistently used the Younger Laboratory to conduct crude single dose studies on lethality and also to assess skin and eye irritation from very short-term exposures. When Jensen published his watershed study in 1966 confirming that extensive PCB environmental contamination had occurred from uncontrolled releases of PCBs from 1930–1966,[50] Monsanto retained another toxicology group: Industrial Bio-Test Laboratories (IBT). The first task for IBT was to evaluate the existing toxicity studies Monsanto conducted prior to 1970 to determine the quality and extent of toxicity information Monsanto had for PCBs. In one of the first toxicology reports produced by IBT (Bates 0531555; TOXSTUDIES0996) the cover page reads (Exhibit 18):[51]

Exhibit 18. Cover Page from IBT Study (TOXSTUDIES0996)[51]



TOXICOLOGICAL STUDIES WITH
POLYCHLORINATED BIPHENYLS

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Polychlorinated biphenyl compounds (PCB's) have been reported to be found in certain birds and in other wildlife samples which have been analyzed. The PCB's represent a family of a number of different compounds, depending upon the amount of chlorination of biphenyl.

Although some toxicological data were available, they were rather limited. Information on chronic effects especially of the PCB's were not available, therefore a number of studies were started to investigate such effects.

This indicates that Monsanto's toxicity information was "limited," which would have been a generous characterization based on my assessment. More importantly, it states that there was *no* chronic toxicity information available, which is consistent with my opinion.

In summary, not one of the studies conducted on Monsanto PCB Aroclors was applicable for long term exposure to PCBs in the workforce or general public.[7] The contract studies only produced information on the lethal dose and short-term irritation—i.e., the quantity of PCBs that could cause death and qualitative information on short-term irritation effects on the skin and eye. Chronic toxicity information is vital for widespread contaminants like PCBs because exposure is

[7] Note, I also reviewed the Treon study, which was poorly designed and implemented such that its results are not helpful.[122] For example, the toxicity of Aroclor 1242 was studied with a hodgepodge of "one cat, 6 guinea pigs, 10 mice, 4 rabbits and 10 rats." Typically, at minimum, 15 to 20 animals would be tested in each species and there would be an equal number of age and sex matched control animals. It is not even possible to calculate the average toxic response for cats with only one cat test animal. Furthermore, many of the test animals were severely ill and suffering from infectious pneumonia which renders the entire study unusable.

chronic throughout a person's entire life from various exposure pathways starting with exposures in the womb and during breast feeding. My analysis of Monsanto's toxicological studies is attached as Appendix C.

4.3.1.1. LD50

The overwhelming majority of Monsanto studies were "lethal dose 50" or LD50 studies. This is a very crude test to determine the lethal dose. An LD50 study, however, is not a toxicity study because it provides no information on the toxicity of a compound; it just establishes the lethal dose. These studies—also known as "dose-them-and-count-them" studies—use a single high dose to kill animals. The LD50 study is so named because laboratory animals are given one single high dose of a chemical and the number of animals that die within 14 days is then counted; that is the end of the study. The LD50 is then calculated by determining the chemical dose that killed 50% of the animals. No cause of death is determined; no pathology is conducted; and there is no urine analysis, no blood analysis, or any other examination on any organ system.

These studies provide no toxicity information and are only directly used by toxicologists in cases of suicides or accidental overdose. The lethal dose is also used to design a dosing regimen for chronic toxicity testing. However, Monsanto clearly did not use the LD50 information for those studies, since they did not produce any chronic toxicity study until 1970. It is unclear how, if at all, Monsanto used this information.

The LD50 study provides such limited information that the Pharmaceutical Manufacturers' Association recommended that the traditional LD50 test be *banned* because too many laboratory animals are killed for studies that yield little or no toxicity information Lebeau (1983).[52] Instead a "range find" test is substituted to delineate an approximate lethal dose with just a few animals.

4.3.1.2. Subchronic Rodent Studies

Subchronic rodent studies are usually 90-day studies and are useful for evaluating relatively short-term exposures, either in the workplace or to the general public. Like the LD50 studies, they are not relevant to toxic effects in members of the general public. Based on my review I

could find no subchronic PCB Aroclor Monsanto study before 1971 and that study was on a chicken—a nonrodent species.

4.4. Throughout the 1940s-1960s, Monsanto misled customers and the public about PCB toxicity and the adequacy of its testing.

Throughout the 1940s–1960s, Monsanto appears to have misled many of its customers about the toxicity of PCBs. Moreover, while Monsanto was warning the chemical industry that toxicity studies should be performed on newly developed compounds, Monsanto did not perform any toxicity studies on PCBs, despite manufacturing hundreds of millions of pounds of the chemical.

In 1947, for example, Monsanto highlighted a recent address from Dr. Kelly (Monsanto's Physician; WASHARCH00015) to the American Public Health Association (APHA).[53] In this address, Dr. Kelly focused on the challenges the industrial chemical field faced with regard to making sure "toxicological investigations" were "keep apace because it is broadening too rapidly." He stated:

> *Although many new products are being developed by manufactures, the problem is to make certain that no new chemical is used in a manner in which systemic toxicity or skin irritation might result either in workers making the product or in consumers.*

While Dr. Kelly specifically urged the chemical industry to ensure that "no new chemical is used in a manner in which systemic toxicity" might result "in consumers," Monsanto itself did not follow Dr. Kelly's advice regarding PCBs. Additionally, Dr. Kelly stated:

> *every new textile chemical developed by Monsanto is subjected to a laboratory study for such reactions culminating in patch testing on 200 human subjects. In plastics, animal experimentation involving, in some cases, two-year feeding tests must be made before they can be marketed. Some substances are so innocuous that they can be used in any application, while the use of others must be more limited.*

This statement is important for two reasons. First, it shows that Monsanto not only had the capability to conduct chronic 2-year animal studies but that it was actually conducting chronic animal studies as early as 1947 for other compounds it was producing. Second, the only way to determine if a compound is "innocuous" is to run toxicity tests to prove it. But Monsanto's very first chronic animal study would have shown chronic PCBs exposures were not innocuous—but rather, were toxic and carcinogenic.

Another example of Monsanto providing misleading toxicity information is a 1950 response letter to Dr. Spolyar (Director of the Division of Industrial Hygiene, Indiana State Board of Health), who had written to Dr. Kelly asking for basic toxicity information on Aroclors. Dr. Kelly responded:[26]

> *The toxicology of Aroclors is somewhat confused. The experimental work done by Dr. Drinker at Harvard about 12 years ago, and was done in connection with chlorinated naphthalene, chlorinated diphenyl, and chlorinated diphenyl high boiler. Both of these last two are Aroclors. In the particular work at Harvard, Dr. Drinker found that Aroclor 1268, which means diphenyl chlorinated to 68%, was of low toxicity. The confusion existed in his findings that Aroclor 1254 which is the diphenyl chlorinated to only 54%, was considerably toxic on inhalation. We did not supply him with this material, and I was never convinced that some error might not have been made in the sample.*

There are several misleading statements in Dr. Kelly's letter. First, he stated, "We (Monsanto) did not supply him [Dr. Drinker] with this material" (referring to PCBs). While that may be true, Dr. Kelly knew that Dr. Drinker was testing Monsanto's PCBs since it produced *all* PCBs in the United States. Second, it shows that, as late as 1950, Monsanto itself was unsure of Aroclor's toxicity yet took no steps to conduct toxicity testing itself to deal with this uncertainty. As I will discuss below, dozens of studies were conducted by 1950 to evaluate the toxicity of DDT, and Monsanto could have addressed this "uncertainty" regarding PCBs by simply following the exact same scientific protocols used in 1945–1950 to investigate DDT. If Monsanto believed Dr. Drinker's PCB study findings in 1937 were corrupted, flawed, or uncertain, Monsanto could have independently conducted its own PCB toxicity studies by 1950, when Dr. Kelly sent this

letter. Third, although the Miller study provided unequivocal findings of PCB toxicity years earlier--in 1944--Dr. Kelly failed to offer that information or even provide a reference to Miller's study.

Even the steps Monsanto took to protect its workers seem to have been belated. While Miller (1944) showed toxicity linked to ingestion of PCBs, Monsanto did not warn its workers until a decade later that they should not ingest PCBs; Mr. Garrett wrote in a 1955 internal memo (MONS093616) that the Medical Department warned that eating contaminated food could lead to "serious difficulties:"[54]

> *It has long been the opinion of the Medical Department that eating in the process departments is a potentially hazardous procedure that could lead to serious difficulties. While the Aroclors are not particularly hazardous from our own experiences, this is a difficult problem to define because early literature work claimed that chlorinated biphenyls were quite toxic materials by ingestion or inhalation. In any case where a workman claimed physical harm from any contaminated food, it would be extremely difficult on the basis of past literature reports to counter such claims.*

In 1963, another customer requested toxicity information about Aroclors. Dr. Kelly's response letter (PCB-ARCHO736677) to Mr. Hempel regarding TK Products Inc. seems misleading:

> *Even though they don't ask for the toxicity, I think we should tell them that these compounds do not possess the long-term toxicity needed for the toxicological clearance and that such clearance probably only can be obtained by showing non-extraction.*

It is not clear why Dr. Kelly would state that PCBs do not possess "long-term toxicity" when Monsanto had never conducted any long-term toxicity tests on any Aroclor; Monsanto did not even have *preliminary* chronic toxicity information until the early 1970s. However, Kelly stated just the opposite in a letter just 4 years later to Mr. Wilde. In his 1967 letter, Dr. Kelly summarized a conversation he had just had with Dave Wood in Brussels about the recently published 1966 Jensen study that suggested PCBs were likely a worldwide contaminant. In that

letter, Kelly admitted there was no chronic toxicity information on PCBs as of 1967 (MONS 096495):[55]

> *The customers would like some reassurance on the toxicity of Aroclor (I explained to Dave that there just was no information available on the action of nanograms of Aroclor in the human body over a lifetime). There is no toxicological work going on at present in Sweden and it appears there is some likelihood that it will not be able to obtain funding and might not be done. Everybody over there is 100% convinced that what Jensen and Widmark found was Aroclor.*

Dr. Kelly admitted that there were no chronic toxicity PCB studies at that point. This highlights the fact that, even though he stated in his 1947 address that 2-year lifetime studies were being conducted by Monsanto for other compounds, PCBs did not merit investigation.

4.5. Monsanto's studies conducted by Industrial Bio-Test Laboratories, Inc. (IBT) would not be held as reliable by a reasonable toxicologist.

Fifty-five of the studies funded by Monsanto were conducted by Industrial Bio-Test Laboratories, Inc. ("IBT"). To the extent they bear on the carcinogenicity of PCBs, those studies are suspect because the results diverge so significantly from other cancer studies conducted by independent scientists in the 1970s and 1980s. Further, the three IBT scientists who oversaw the Monsanto PCB cancer studies (Drs. Paul Wright, James Plank, and M.L. Keplinger), were indicted and convicted of mail fraud, wire fraud, and making false statements because they submitted to the FDA false results of studies they conducted for Monsanto and another client for other non-PCB chemicals (https://www.courtlistener.com/opinion/460360/united-states-v-moreno-l-keplinger-paul-l-wright-and-james-b-plank).[56] And Philip Smith, an assistant toxicologist with IBT beginning around 1971, admitted in trial testimony that IBT falsified data

in long-term, chronic toxicity tests performed on rats using Aroclors 1242, 1254, and 1260. (WATER_PCB-00056547–56623).[8]

The IBT debacle is well known with the field of toxicology as most toxicologists receive training in ethics and professional responsibility. The IBT story involves hundreds of fraudulent studies that were submitted to U.S. regulatory agencies. For example, IBT produced 801 toxicity studies of pesticides,[56] and their reports were submitted to EPA to show that those pesticides were safe. Following the discovery of IBT's false data during the trial of the three IBT scientists, EPA conducted a re-review of the IBT reports and found that 594 of those studies were invalid (74%) because they contained false or fraudulent data or information.

Although the fraud conviction did not relate directly to Monsanto's PCB studies, the Monsanto studies did not undergo an independent analysis. Additionally, the EPA has shown a reluctance to rely on IBT's PCB studies given the "suspicion with which their data are regarded." EPA, Proposed Rule, Toxic Chemical Release Reporting; Community Right-To-Know, 52 FR 27226-01 (July 20, 1987).[9]

Furthermore, Monsanto pressured IBT to change conclusions of their Aroclor cancer studies. Starting in 1970, the IBT laboratory prepared and sent several draft reports to Monsanto that presented the number of tumors that were found after rats were exposed to Aroclor 1260, 1254, and 1242. They also stated their overall conclusions about how the Aroclors should be classified as to being either carcinogenic or noncarcinogenic. IBT originally classified the tested Aroclors as "slightly tumorigenic." After reviewing the draft reports, Monsanto requested that IBT alter the language to "does not appear to be carcinogenic" and IBT agreed. This is shown in a July 18, 1975 Monsanto Memo from Dr. Levinskas (Monsanto's Manager of Environmental Assessment and Toxicology) to Dr. Calandra (President of IBT) where Levinskas unilaterally altered the IBT conclusion. Whereas IBT stated in the draft report Aroclors were "slightly tumorigenic"

[8] Note, Monsanto's Elmer Wheeler stated in a February 23, 1973 letter that the studies performed by IBT created data "which has led the government agencies to permit the continued but restricted use." MONS 092758.
[9] The FDA also decided not to rely on IBT's studies, explaining that "doubt has been cast" on studies by IBT. FDA, Final Rule, Polychlorinated Biphenyls (PCBs); Reduction of Tolerances, 44 Fed Reg 38330 (June 29, 1979) at p. 3833.

Monsanto misrepresented the carcinogenicity to "does not appear to be carcinogenic:" (MONS 093565):

> *Dear Joe:*
>
> *The attached table* [attached to the memo] *summarizes a comparison of the 3 revised AROCLOR [sic] reports (1242, 1254, 1260).*
>
> *In 2 instances, the previous conclusion of "slightly tumorigenic" was changed to "does not appear to be carcinogenic." The latter phrase is preferable.* [emphasis added]

It is highly unusual and irregular for a chemical company to unilaterally alter the findings or conclusions reached by their own experts or contract laboratories conducting toxicity tests on their products. If Monsanto had requested IBT to make a revision based on a technical or scientific issue, it would perhaps be understandable (depending on the reason). However, according to the memo, no scientific explanation was given for the change and Monsanto simply directed IBT to alter the report. In Monsanto's view, their phrase was simply "preferable."

Altering the IBT cancer classification of PCBs should not be considered a minor "tweak." Rather, Monsanto changed the classification of PCBs from a carcinogen to a non-carcinogen. When chemicals undergo animal cancer testing, a two-step process is always followed. In the first step, a determination is made whether a chemical is a carcinogen or not. This is a yes-or-no determination. If a chemical is determined to be a carcinogen, then and only then, is the dose response relationship evaluated to determine its cancer causing potency. That is, a determination is made to evaluate it potency as a "slightly, moderately, or very potent carcinogen." Instead of following this standard two-step process, Monsanto in the very first step concluded PCBs were not carcinogenic. Obviously, this precluded a further determination of the cancer potency in the second step.

Monsanto made these changes in classification despite the fact that all the Aroclors caused focal hyperplasia and tumors. Exhibit 19, which is presented in the Monsanto memo, shows the number of tumors that were detected in the IBT cancer tests. It also shows the changes they

directed IBT to make, altering the classification of each Aroclor to read "does not appear to be carcinogenic:[51]

Exhibit 19. Tumors Detected in IBT Cancer Tests

Product	Supplemental Report #1 (mailed)	Supplemental Report #2 (JCC delivered)
AROCLOR 1260		
conclusion	slightly tumorigenic	does not appear carcinogenic
hepatomas	3	7
range of test animal nos:		
p. 9	600 to 800	100 to 300
p. 10	1000 series	800 to 900
p. 11	70 to 100	10 to 40
p. 12	500 to 600	80 to 200
p. 13	600 to 700	200 to 300
p. 14	700 series	200 to 300
AROCLOR 1254		
conclusion	slightly tumorigenic	slightly tumorigenic
hepatomas	6	6
AROCLOR 1242		
conclusion	slightly tumorigenic	does not appear carcinogenic
hepatomas	7	3
range of test animal nos.	as in report #2 for AROCLOR 1260	as in report #1 AROCLOR 1260

From the table, it is clear that the Aroclors produced hepatomas in each case. Despite this clear evidence of tumors, Monsanto chose to arbitrarily change the cancer classification.

I have also reviewed a trial transcript dated 10.28.1991 that presents testimony by Mr. Philip Smith pertaining to Monsanto's IBT 1970 PCB chronic toxicity studies. Mr. Smith testified that he was an assistant toxicologist with IBT and actively participated in IBT's PCB studies. Mr. Smith admitted that IBT falsified data, information, and conclusions in these studies.

Mr. Smith first testified to participating in generating falsified rodent body weight. During any toxicological testing protocol, body weight is always carefully measured because it provides very important information about the overall health of rodents. Because necropsy examinations cannot be carried out during the 2-year period, body weight is the best and most insightful proxy data that provides a window into a rodent's health. Accordingly, it is critical to weigh the animals frequently to monitor their health as well as food and water intake. Mr. Smith testified that "a lot of the body weight data" was missing and he was instructed to take all the rodent weight data that the laboratory had amassed and graph it, and then his superior, Dr. Wright, made up false weights for the missing data. These false data were inserted into the final IBT PCB reports submitted to Monsanto.

Additionally, Mr. Smith testified that the PCB-dosed rats' survival rate was "[v]ery poor," and he estimated it was less than 10 percent or less. Furthermore, some of that data was never recorded in laboratory notes and false survival rates were entered into the final study. No necropsies were performed on the dead animals due to advanced decomposition, which precluded pathological examination or a determination of the cause of death. There was also no record of the dead animals entered into the laboratory records so it was as if the animal had never been in the study and according to Mr. Smith they just "disappeared."

Based on Mr. Smith's testimony, the Aroclor study results and conclusions lack veracity and should not be considered as probative evidence for any conclusions IBT and Monsanto reached regarding PCB carcinogenicity. Moreover, all Monsanto subsequent presentations, publications, communications that relied on the falsified IBT cancer study findings should be disregarded as unreliable.

Given the differences between the IBT studies and other published animal cancer studies, the history of fraudulent activity at IBT, and admissions that IBT falsified data during PCB toxicity studies, a reasonable toxicologist would not hold the IBT studies as reliable studies.

Book 2

5. EXECUTIVE SUMMARY

Based on common scientific knowledge established by the late 1800s and routinely utilized in the scientific community for decades thereafter, Monsanto had all necessary information on the physicochemical property of PCBs by as early as 1945, and no later than 1950, to predict that PCBs would bioaccumulate and biomagnify in animals and humans.

Well before Monsanto began producing PCBs, the scientific community predicted bioaccumulation of a chemical based on the oil-water partition coefficient. By 1945, empirical evidence from actual environmental exposures to DDT was published. These studies confirmed that highly lipophilic compounds bioaccumulated and biomagnified in the food chain. By at least 1945, Monsanto must have known that DDT and PCBs were nearly equal with regard to lipid solubility (and thus would similarly bioaccumulate & biomagnify) because Monsanto was manufacturing both DDT and PCBs in 1944. The company also must have known from published DDT studies that bioaccumulation and biomagnification of DDT were solely governed by the physicochemical property of lipid solubility. This fact was known throughout the chemical industry. In addition, Monsanto must have known that both DDT and PCBs, due to their similar chemical structures, were extremely stable compounds and would be equally resistant to degradation and, therefore, both would be highly persistent when released into the environment.

Based on the similar lipid solubilities of DDT and PCB, and the overwhelming empirical evidence that had amassed for DDT, it is my opinion that Monsanto could have predicted and correctly concluded that PCBs would bioaccumulate and biomagnify in fat tissues of all animals and humans to essentially the same magnitude reported for DDT studies published in 1945–1950. For these and other reasons stated in this report, Monsanto must have known by 1945-1950 that its PCBs posed a significant risk of environmental persistence, bioaccumulation, and biomagnification in animals and humans.

6. MONSANTO MUST HAVE KNOWN THAT PCBS WOULD BIOACCUMULATE AND BIOMAGNIFY BASED ON LIPID SOLUBILITY.

In this section, I present evidence to support my opinion that Monsanto must have known during 1935–1950 and thereafter that its polychlorinated biphenyls (PCBs; Aroclors) would bioaccumulate in animals and man. In this report, I define bioaccumulation as a gradual increase in PCB body burden that results from the net between absorption of PCB into the body minus its elimination from the body. When rate of intake and absorption of PCBs into the body exceeds the rate of excretion from the body, PCBs bioaccumulate with continued exposure. The body burden is the net sum of PCBs measured in the body at a particular point in time. PCBs bioaccumulate primarily in fat (adipose) tissue and in fat-rich cell membranes because PCBs are highly fat- or lipid-soluble compounds.

This opinion is based a careful reconstruction of the state of the science in the late 1800s and early 1900s regarding the physicochemical property of lipid solubility. This property was known to be the sole property responsible for the absorption of fat-soluble chemical compounds like PCBs through cell membranes and, ultimately, their sequestration in fat-rich tissues and membranes. As I will detail in this section, the theory for this physiological phenomenon was first postulated in the late 1800s; with each passing year, experiments solidified it into a scientific "rule." By the early 1900s, scientists were applying this rule to make predictions about the degree to which compounds would preferentially be absorbed into animals (based on the partitioning between oil and water). To reconstruct the chronological sequence of studies that ultimately led to scientists to predict bioabsorption of organic chemical compounds, I reviewed approximately 70 historical peer-reviewed studies starting in the mid-1880s through 1945. I also examined historical reviews recently published by experts in the field. These contemporary scientists have compiled histories consistent with the one I present in this report.

The scientific industry understood principles of bioaccumulation well before Monsanto began producing PCBs. Therefore, Monsanto must have known that PCBs would bioaccumulate from

the time it began manufacturing PCBs. A summary of facts supporting this opinion is as follows:

A. The lipid solubility of a chemical was an easy physiochemical parameter to measure in the laboratory and was the only physical measurement needed to predict uptake and bioaccumulation in aquatic and terrestrial animals.

B. The lipid solubility of numerous and diverse organic chemical compounds was quantified in the laboratory by the *oil–water partition correlation coefficient,* which described the relative degree of partitioning of a compound between oil and water.

C. The first use of the oil–water partition coefficient to predict and quantify bioaccumulation in animals occurred in the late 1800s.

D. The partition coefficient was the predominant property governing bioaccumulation in laboratory animals in the late 1800s; it was identified as the sole physicochemical property governing drug effects and toxicity.

E. Aquatic organisms were the first animals tested in the late 1800s to determine the oil-water partition coefficients.

F. By the 1930s and 1940s, lipid solubility was the primary physical property used by scientists to make predictions and comparisons regarding bioaccumulation in biological systems.

G. Monsanto must have known by 1929 (when Swann Research Company started production) that PCBs were highly lipid soluble because the company referred to them as *oils* in its original patent that was granted.

H. Any independent, competent scientist in the 1930s would have predicted PCBs were bioaccumulative based solely on the knowledge that they were highly lipid soluble and, therefore, would accumulate in cell membranes and fat stores; no further chemical-specific information was needed to make this prediction.

I. Monsanto must have known in 1935 that PCBs were extremely stable compounds based on their chemical structure and the strong chlorine-bond, which was resistant to degradation; based on this stability, Monsanto could have predicted that PCBs would be extremely persistent in the environment.

The analysis I present in this section focuses specifically on the oil–water partition coefficient as the single physical property that was used through the year 1944 to make predictions regarding bioaccumulation. I reconstruct the time period of approximately 1944–1955 to show how scientists verified their earlier predictions based on lipid solubility and partition coefficients by conducting environmental studies based on empirical data that proved their early predictions. In this section, I focus on one of the most notorious bioaccumulative and biomagnifying chemical compounds first identified as a ubiquitous and worldwide contaminant: dichlorodiphenyl trichloroethane (DDT)—a product that Monsanto manufactured starting in 1944. In this report, I define biomagnification as the accumulation of organic compounds (e.g., PCB and DDT) by animals and humans from chemical intake that results in a body burden that is greater than the intake concentration. This describes the increase or magnification of the body burden at each trophic level moving up the food chain. Because humans sit at the apex of the food chain, the body burden will be highest in man.

I opine that Monsanto must have known by 1950 that PCBs bioaccumulate and biomagnify. A summary of facts supporting this opinion is as follows:

A. The scientific community utilized the lipophilic property of organic chemical compounds to predict bioaccumulation in biological animals;

B. DDT and PCBs were similar chemical compounds possessing high lipophilic properties;

C. Empirical evidence had accumulated to prove DDT bioaccumulates in fat tissue and biomagnifies as it moved up each successive step in the food chain; and

D. Based on the similar lipid solubility of PCBs and DDT and the empirical evidence that had amassed by 1950 proving that DDT bioaccumulated and biomagnified in the food chain, Monsanto must have known that PCBs would likewise bioaccumulate and biomagnify in animals and humans.

6.1. For over 130 Years, Lipid Solubility Has Been Key to Determining the Potential for Bioaccumulation.

This section presents evidence of the pivotal role that lipid solubility plays in predicting bioaccumulation. It is the sole physicochemical property determining the potential for bioaccumulation, and it has been used for more than 130 years to predict bioaccumulation in biological systems.

In the environment, lipid-soluble organic chemical compounds partition into the fat tissue of biological receptors—particularly those in aquatic environments. Once an organism bioaccumulates lipid-soluble compounds, those compounds are biomagnified when eaten by a predator in the next trophic level. Since humans occupy the apex position in the food web, we have the highest bioaccumulation and body burdens of lipophilic chemical compounds. Finally, pregnant mothers transfer lipophilic compounds across the placenta and continue to expose suckling newborns to high concentrations of lipophilic compounds, ultimately rendering young children the most-exposed group in this long bioaccumulative chain (based on body weight). Young children are truly the apex group.

Lipid-soluble (also called *fat-soluble* or *fat-loving*) compounds bioaccumulate because they enter cells through passive transport. Membranes of all biological systems are made up of a lipid bilayer. Once lipid-soluble compounds are absorbed into the body, they are transported in blood bound to lipoprotein carrier molecules and are then distributed to fat tissue, where they are stored. These physiological phenomena of absorption, distribution, and storage can be predicted, and the magnitude estimated simply based on the lipid solubility of a chemical compound.

The solubility in lipid is compared to a chemical's solubility in water and was initially defined as the *oil–water partition coefficient* because scientists used olive oil and water (today, this is known as the *octanol-water partition coefficient* because the distribution is measured in the laboratory using octanol and water). While the nomenclature has changed over the 130 years since the concept was first defined, the principle has remained the same and has been used to predict the bioaccumulation in terrestrial and aquatic animals, as well as in humans. Accordingly, I will use all of these terms interchangeably in this report.

The oil–water partition coefficient (or, *partition coefficient*) is a fundamental physicochemical property of all chemicals. Some chemicals preferentially dissolve in water, while others preferentially dissolve in lipid. By measuring how a chemical partitions between oil and water, scientists can predict how a newly synthesized chemical will partition into membranes and fat compartments of the body versus the water compartments. Thus, the partition coefficient is one of the most fundamental and basic laboratory analyses that, together with the boiling point and vapor pressure, is measured for all newly synthesized industrial chemical compounds. In fact, the partitioning coefficient is a *required* chemical parameter that *must* be determined to comply with U.S. and E.U. regulations as I discuss below.

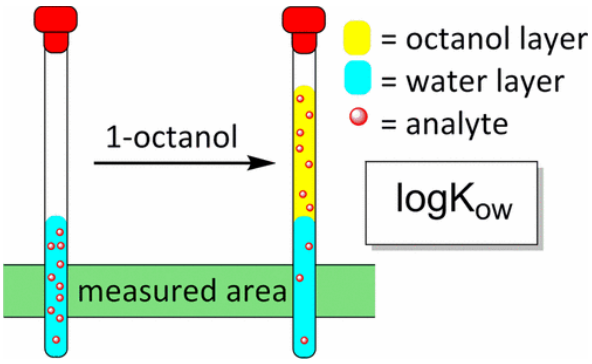
However, it is not always necessary to conduct an actual partitioning laboratory experiment if the compound is highly lipid soluble and virtually insoluble in water (like PCBs). It is only necessary to calculate the oil-water partitioning coefficient for compounds that are on the *margins* where a compound is miscible in both oil and water to some degree. That is, the measurement need only be conducted on those compounds when there is some uncertainty in how it precisely partition between oil and water. When a compound is extremely lipophilic, such a measurement need not be carried out to make predictions about its fate and transport in the environment.

Based on Monsanto's chemical description of PCBs, it must have known that PCBs were not miscible in water and were highly lipophilic compounds. For example, in its 1944 sales brochure (MONS092683),[57] Monsanto stated that the solubility of water in Aroclor 1242 was 0.08% which (indicates that PCBs and water were essentially immiscible), while it was extremely

miscible in many organic (lipophilic) industrial solvents like benzene. Thus, the oil-water partition coefficient for PCBs would be so high that an actual measurement was unnecessary.

The oil–water partition coefficient analysis is easy to measure and requires no special laboratory equipment. It is such a basic and fundamental physicochemical property that most undergraduate students taking a course in organic chemistry are taught how to conduct such analyses early in their academic training. It simply involves adding a test chemical compound to a vessel or test tube containing equal parts oil or octanol and water, mixing the solution, and then allowing the solution to equilibrate; the chemical concentration is then measured in each of the oil and water phases. The simple steps in this measurement are shown in Exhibit 20 below:

Exhibit 20. Oil–water Partition Coefficient Analysis



Source: Cumming and Rücker 2017.[58]

A chemical compound's oil-water partition coefficient was measured in the late 1800s and early 1900s to characterize how numerous industrial organic solvents and drugs would accumulate in animals and the human body. By the early 1900s, this was known as the "Meyer-Overton Rule" (Perouansky, 2015).[59]

The importance of this single physical property cannot be overstated. It is now commonly used as the basis for the development of environmental regulations, as well as for human health and ecological risk assessments. For example, guidance for deriving the partition coefficient, which is known as the Kow, was standardized by the U.S. National Bureau of Standards for the U.S.

Environmental Protection Agency (EPA) more than 30 years ago so that diverse chemical compounds could be characterized in order to make predictions about their potential to bioaccumulate. Furthermore, numerical risk-based screening concentrations presented in regulatory guidance documents like the U.S. EPA's Soil Screening Levels tables were developed for the Superfund Program so they could be used to predict fate and transport of each organic compound at thousands of sites to track the movement of pollutants through the environment.[60], [61]

In addition, U.S. EPA's Office of Prevention, Pesticides and Toxic Substances' specific guidelines for testing pesticides emphasizes the importance of the partition coefficient:[62]

> *(ii) In the study of the environmental fate of organic chemicals, the octanol/water partition coefficient has become a key parameter. It has been shown to be correlated to water solubility, soil/sediment sorption coefficient, and bioconcentration. The importance of this property to SAR [structure activity relationships] is indicated by its discussion in the first chapter of Lyman, Reehl and Rosenblatt's (see paragraph (e)(11) of this guideline). These authors consider the measurement or estimation of the octanol/water partition coefficient to be the* <u>necessary first step</u> [emphasis added] *in assessing the fate of chemicals.*
>
> *(iii) Of the three properties that can be estimated from Kow, water solubility is the most important because it affects both the fate and transport of chemicals. For example, highly soluble chemicals become quickly distributed by the hydrologic cycle, have low sorption coefficients for soils and sediments, and tend to be more easily degraded by microorganisms. In addition, chemical transformation processes such as hydrolysis, direct photolysis, and indirect photolysis (oxidation) tend to occur more readily if a compound is soluble.*

The critical importance of identifying fat-soluble compounds to predict bioaccumulation is not limited to the United States. The European Union's chemicals legislation, *Registration, Evaluation, Authorization and Restriction of Chemicals* (REACH), also requires the

determination of the oil–water partition coefficient for every new chemical compound manufactured or imported in amounts ≥ 1 ton/year.[63] The European Union enacted REACH to address and prevent further environmental contamination. REACH puts the burden on the chemical industry to identify bioaccumulative industrial compounds, prove they are safe to use, and prove they will not cause widespread contamination.[64]

The REACH regulations state that the oil–water partition coefficient is the most important parameter to gauge absorption into biological systems; this parameter is known as Kow or, more specifically, the log of the Kow or log P.[10]

A Kow value of 1.0 indicates that a chemical compound is equally distributed oil and water (the log of Kow = 1 is zero). As the fat solubility increases for a group of chemical compounds, the Kow (or log P) increases concomitantly. The REACH defines a highly lipophilic compound that will bioaccumulate as log P = 4. A partitioning ratio or log P equal to 4 indicates that the compound will be soluble in octanol 10,000 greater than water (the ratio is 10,000:1). For comparison purposes, all Aroclors have log Kow values > 4.0 so they would be defined by REACH as highly bioaccumulating compounds that would be regulated. As shown in Exhibit 21 below, the range of PCB log Kow values increases with increasing chlorination of the mixture of PCB congeners from 4.7 to 6.8. This demonstrates that Monsanto's Aroclors have high bioaccumulation properties.

Exhibit 21. Aroclor Kow Values

Octanol-water partition coefficient	Aroclor 1221	Aroclor 1232	Aroclor 1016	Aroclor 1242	Aroclor 1254	Aroclor 1260
Log Kow	4.7	5.1	5.6	5.6	6.5	6.8

[10] Log P is equal to log Kow and is sometimes used instead of Kow because it conveniently converts the oil-water partition values to a log scale. For example, log P = 0 is equal to 1. The log P values of 1–4 represent the Kow (oil water partition coefficient) equal to 10:1 (log P) to 10,000:1 (log P) parts oil:water.

Source: ATSDR 2014.[65]

The Agency for Toxic Substances and Disease Registry (ATSDR) has also gathered information on the log Kow values for individual PCB congeners because PCBs constitute some of the most persistent chemicals that are routinely detected in human blood. Examples of log Kow values for five PCB congeners that have increasing degrees of chlorination are presented in Exhibit 22.

Exhibit 22. PCB Kow Values

Oil–water partition coefficient	PCB 77	PCB 138	PCB 153	PCB 169	PCB 180
Log Kow	6.04–6.63	6.50–7.44	8.35 6.72	7.408	6.70–7.21 (calc.)

Source: ATSDR 2014.[65]

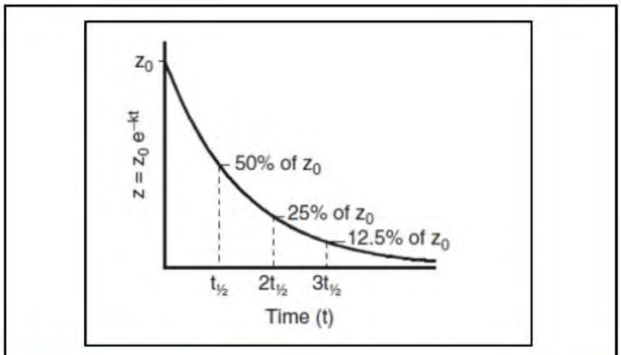
The REACH regulations also note that, in addition to providing information on bioabsorption in the environment, the Kow is used to predict bioaccumulation that results from chronic exposures when elimination from the body is slow because of the chemical-specific *half-life*. That is, with each subsequent exposure (or continuous exposure over time), the lipophilic organic compound builds up in fat tissue and membranes because it is not be eliminated. When bioaccumulation exceeds elimination, body burden increases. The European Union concluded that the Kow threshold for bioaccumulation is 4.0:[63]

> *Lipophilic substances have the potential to accumulate within the body if the dosing interval is shorter than 4 times the whole body half-life. Although there is no direct correlation between the lipophilicity of a substance and its biological half-life, substances with high log P values tend to have longer half-lives unless their large volume of 10 distribution is counter-balanced by a high clearance. On this basis, there is the potential for highly lipophilic substances (log P >4) to accumulate in individuals that are frequently exposed (e.g. daily at work) to that substance.*

REACH regulations focus on workers with their example of "daily at work" values utilized in chemical industry exposures. However, this issue is of critical importance to the general population when there are widespread environmental exposures that can lead to contamination of the food supply and the general population.

The concept of the chemical half-life is based on the time it takes for 50% of a chemical compound to be eliminated from the body (assuming exposure stopped at time zero and it follows a first-order elimination constant). This is illustrated in Exhibit 23.[66] As shown, it actually takes about 10 half-lives for the chemical to be *completely* eliminated from the body (assuming first order rate elimination kinetics). As a practical example, if a newborn child bioaccumulates a lipophilic organic chemical compound in the womb as a fetus, and then during breastfeeding, and that compound has a half-life of 5 years, it would take approximately 50 years for the entire dose to be eliminated from the body after the newborn has been weaned throughout its life (assuming that there is no further subsequent exposures).

Exhibit 23. It Takes About 10 Half-Lives To Eliminate Chemical From Body



Time (t)	Percent of Initial Value	Percent Completion
$t_{½}$	50%	50%
$2 \cdot t_{½}$	25%	75%
$3 \cdot t_{½}$	12.5%	87.5%
$4 \cdot t_{½}$	6.25%	93.75%
$5 \cdot t_{½}$	3.125%	96.875%
$7 \cdot t_{½}$	0.781%	99.219%
$10 \cdot t_{½}$	0.098%	99.902%

Source: Byers and Sarver 2009.[66]

The half-lives for different Aroclors and PCB congeners varies. For example, Exhibit 24 from ATSDR shows the "Apparent Half-lives" for individual PCB congeners:[67]

Exhibit 24. Apparent Half-lives of Aroclors and PCB congeners

Table 3-10. Apparent Half-lives (Years) of PCB Mixtures from Multiple Studies

Mixture	Elo et al. 1985	Hara 1985	Phillips et al. 1989	Steele et al. 1986[a]	Taylor and Lawrence 1992	Wolff and Schecter 1991[b]	Wolff et al. 1992[c]	Yakushiji et al. 1984	Yakushiji et al. 1984
Clophen A30	0.02								
Kanechlors									
300		5.1							
300/500		>15						0.67	7.1, 2.8[e]
Aroclors									
1242			2.6	2.0	1.8	0.9, [f]			
1248							8.6		
1254			4.8		3.3		65		
1260				27.6	4.1	1.2, 0.5[g]			

Congener	Brown et al. 1989	Buhler et al. 1988	Chen et al. 1982[a,c]	Chen et al. 1982[a,c]	Luotamo et al. 1991[d]	Luotamo et al. 1991[e]	Ryan et al. 1993[f]	Wolff and Schecter 1991[g]	Wolff et al. 1992[h]	Yakushiji et al. 1984
153	12.4	0.93	47	26		••	3.8		•[i]	27.5
105	3.9		0.58	0.51					•[i]	
138	6–7	0.88	32	20			3.4		16.7	16.3
163	>20									
183						0.13			7.9[j]	
128			5.2	5.4					7.9[j]	
171						0.08			24	
156			•	•	•	•	4.0			
180		0.34	•	•	•	•	4.3			9.9
169							10.4			
170			47	71			3.9			

Source: ATSDR 2000.[67]

Based on these tables, it appears that as the lipid solubility of an Aroclor increases the half-life also increases. For example, both Philips et al. (1989) and Taylor and Lawrence (1992) show that Aroclor 1254 is eliminated from the body slower than Aroclor 1242. Aroclor 1254 is more lipid soluble than Aroclor 1242 based on their respective Log Kow values, which are 6.5 and 5.6.

Independent from the regulations, the European Union has adopted testing procedures that are as restrictive as the official REACH regulations and has put into place industrywide procedures to predict which industrial chlorinated compounds have the potential to bioaccumulate. These testing procedures focus on lipid solubility as the property that is most important for screening of all new chemicals (as do the REACH regulations).

For example, Euro Chlor, an industry group representing chlor-alkali producers in the European Union and European Free Trade Association (EFTA) regions (which employ about 39,000 people at 69 manufacturing locations with almost 2,000,000 jobs in Europe) is intent on precluding both bioaccumulation and biomagnification in the food web:[68]

> *A particular concern attaches to substances that might 'biomagnify', such that the levels steadily increase in food webs from prey to predator (secondary poisoning) so the highest levels are found in animals at the top of the food chain (including humans). Complicating factors in the assessment of biomagnification are the increasing lipid content of higher organisms and changing lipid content of organisms over the year.*

Euro Chlor recognizes that it is imperative to screen all newly synthesized compounds using "simple" laboratory analyses or computer modeling in order to predict which will bioaccumulate:

> *It is often possible, however, to 'screen' substances on the basis of some simple physical and chemical properties, or using computer modelling, to exclude the majority of substances from further consideration as they clearly do not have any potential to bioaccumulate, or to prioritise substances which appear to have the greatest potential to pose a risk.*

One of the first analyses the group recommends is calculating the log Kow:

> *The octanol/water partition coefficient is an important bioaccumulation parameter that can be used as a surrogate measure to indicate or exclude the intrinsic potential of an organic substance to be taken up in fatty tissues*.

In summary, this section presents evidence of the pivotal role lipid solubility plays in predicting bioaccumulation. It is the sole physicochemical property determining the potential for bioaccumulation. As explained further in the next section, lipid solubility is not a new concept; it has been used for more than 130 years to predict bioaccumulation in biological systems. The importance of this single physical property cannot be overstated as it is largely the basis for the development of environmental regulations regarding lipid-soluble substances.

Monsanto must have known that PCBs were highly lipophilic from the time it began producing PCBs. PCBs were described in the early 1931 patent (originally filed in 1929) as "oils" by Swann Research Inc., indicating lipophilicity.[69] Later, when characterizing the physical properties of PCBs, Monsanto described them as being soluble in numerous organic solvents and as being virtually insoluble in water (MONS092683).[57] Monsanto's own descriptions of its PCBs correctly defined them as highly lipid-soluble compounds, and PCBs would have been recognized as such in the 1930s by independent and competent scientists.

6.2. Chronological History 1880s-1945: Oil–Water Partition Coefficient and the Meyer-Overton Rule

This section addresses the question of whether Monsanto should have predicted or foreseen that lipid-soluble PCBs could bioaccumulate in biological systems if PCBs were released into the environment during the early period of their production (1935–1945). In order to answer this question, I have examined approximately 70 peer-reviewed studies published in 1850–1945 as a state-of-the-science framework from which to form my opinion.

I began by identifying the seminal studies that would have been used to define the concept of the oil–water partition coefficient. I then proceeded to establish the time period when the oil–water partition coefficient was used in diverse scientific disciplines as a predictive scientific tool to identify which new compounds were absorbed by animals and aquatic organisms. I ended my research on this topic in 1945, at which time it was no longer necessary for Monsanto and others in the chemical industry to rely solely on the partition coefficient because empirical evidence of bioaccumulation and biomagnification was now well established with numerous studies on DDT

that were published during 1945–1950. At this point, it became necessary only to identify chemical compounds that had a lipid solubility similar to that of DDT. After these DDT studies were published, the only question remaining was how similar PCB was to DDT in terms of lipid solubility; if similar, Monsanto must have expected PCBs to bioaccumulate and biomagnify in similar ways. I also reviewed early Monsanto documents, patents, and peer-reviewed publications to analyze when the company first acknowledged that PCBs were lipid-soluble compounds.

My review revealed that the concept of organic substances partitioning between oil and water was a well-known physicochemical property of all chemicals as early as the 16th century. In fact, it seems as though the concept was developed from simple common sense and direct observation, almost akin to the discovery of gravity.

Diluting chemicals and substances in "like" solvents may have first been described by Paracelsus (Philippus Theophrastus Aureolus Bombastus von Hohenheim), who is regarded as the father of toxicology.[70] Kenndler and Maier (2018) traced the history of scientists and physicians first conceptualizing that idea that chemicals dissolve in solvents having similar properties.[71] Paracelsus is commonly thought to have noted that "likes dissolve likes," which as most student chemists are taught comes from "similia similibus solventure." *Likes dissolve likes* simply means that lipid-soluble compounds dissolve in lipids:

> *Such selections are often guided by the well-known rule-of-thumb "similia similibus solvuntur" concept, which may be understood as the three-word essence of the Rohrschneider's polarity classification. It appears to have been formulated in analogy to the principle "similia similibus curantur", attributed to Paracelsus, and "similia similibus curentur", a motto of homoeopathy (for the source of the solubility rule see J.H. Hildebrand, R.L. Scott, The Solubility of Nonelectrolytes, ACS Monograph No. 17, Reinhold Publ. Corp., 1950).*

The practical application of likes dissolves likes formed the basis for the separation of mixtures of chemicals based on their different solubilities (and is the basis of the field of chemical and gas

chromatography) and is thought to have originated in the early 16th century. In establishing the date of the first laboratory procedure applying differential solubilities, Kenndler and Maier (2018) traced it to 1512:

> *A curiosity in the history of partition GC is the first traceable separation apparently based on gas liquid chromatography and described as early as in 1512, in the period between the Late Middle Ages and the early modern age, by Hieronymus Brunschwig (ca. 1450 - ca. 1512), in his book "Liber de arte Distillandi de Compositis. Das buch der waren kunst zu distilieren die Composita"(the title page of this book is shown in Figure 3)." (Gas Chromatography and Analysis of Binding Media of Museum Objects: A Historical Perspective. Substantia 2(2): 93-118. doi: 10.13128/substantia- 64, 2018.)*

Kenndler and Maier described Brunschwig's experiment in which he used olive oil to separate ethanol (lipid-soluble) from water as follows:

> *Brunschwig, a German surgeon and botanist, describes a procedure in which the vapor from a mixture of alcohol and water was forced through a sponge moistened with olive oil, and was leading to the recovery of a small quantity of pure alcohol. Expressed in modern terminology, this technique represents a separation process based on frontal GLC, with the oil acting as a liquid stationary phase, the sponge as a porous supporting material, and the alcohol vapor as mobile phase.*

They also presented a simple laboratory apparatus prepared by Tswett in his first experiment applying the concept of the partition coefficient to separate organic (lipid-soluble) compounds from solid matter in the early 1900s:

> *In his first publication from 1903 Tswett, a Russian botanist, described the successful separation of plant pigments. In his experiments, he applied a chlorophyll extract in ligroin (i.e. petroleum ether) at the top of a vertically arranged cylindrical glass tube (see Figure 2) filled with particles of a solid material with adsorptive abilities, and continued*

applying fresh ligroin. Tswett observed the formation of separated colored rings, which migrated through the tube and broadened during their migration.

Kenndler and Maier showed the chemical equipment Tswett used to dissolve the fat-loving chemicals (Exhibit 25).

Exhibit 25. Tswett's Chemical Equipment for Dissolving Lipid-Soluble Chemicals

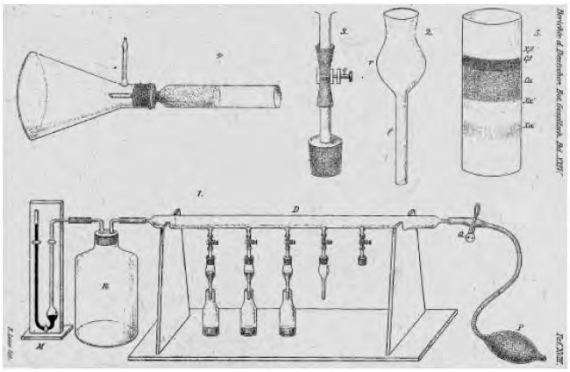


Figure 2. Tswett's device with four packed chromatographic glass columns. Drawing (1.): three columns filled with adsorbents for the separation of plant pigments. The columns had an inner diameter of 2-3 mm, and a length of 2-3 cm. Drawing (5.): Separated zones of 5 colored plant pigments (Chlorophylls and Xanthophylls) in a chromatographic packed column. From ref. [9] with permission.

Source: Kenndler and Maier 2018.[71]

The first investigations quantifying the oil–water partition coefficient focused on industrial organic solvents and organic compounds were reconstructed by Sangster (1997),[72] who described the key chronological milestones of research into this subject. He noted that the physicochemical property was first investigated as early as 1872 by Bertholet and was then independently investigated by Nernst in 1891.

The first oil-partition coefficient experiments on industrial compounds relied on symptoms of narcosis and toxicity as the endpoints. That is, to determine the degree of absorption and bioaccumulation into the bodies of terrestrial and aquatic animals, the toxic effects were observed, and the absorption was graded depending on the magnitude of the narcosis response.

An increasing narcotic effect represents an increase in absorption. Organic compounds are still studied today by evaluating narcosis and the compound's lipid solubility. Narcosis follows a dose-response curve that is solely dependent on the lipid-solubility of organic compounds, whereby the chemical dissolves into the neuronal membrane and attenuates or blocks propagation of the electrical nerve signal in the central and peripheral nervous systems.

It should be emphasized that, although these organic chemicals were originally labeled *narcotic* compounds, these were actually industrial organic solvents that had recently been isolated from coal tar and petroleum products and used by chemical companies like Monsanto to dissolve chemical compounds, like PCBs (MONS092683).[57] These narcotic compounds included widely used solvents such as benzene, toluene, long chain alkenes, and hexane, which Monsanto identified as excellent solvents for PCBs.

In early oil–water partition experiments, symptoms and endpoints of narcosis included an animal's lethargy, stupor, drowsiness, delayed reactions, partial or total paralysis, and—with higher doses—death. It was easy to correlate an incremental decrease in motor movement with an increase in dose. A standardized scale could also be developed to compare different compounds with regard to the dose that results in complete paralysis.

The research in the late 1800s and early 1900s on narcotic compounds was not intended to study narcosis, but to categorize lipid-soluble solvents based on their ability to absorb into lipids based on the oil–water partition coefficient. Sangster described this work (1997):

> *Meyer (1899) and Overton (1899) independently reported that narcosis potency was governed not by water solubility but by partition coefficient. Meyer's conclusions were based on careful measurements of partition coefficients in his laboratory by Fritz Baum (1899) for a series of 11 anesthetics of diverse chemical structure using purified olive oil.*

Meyer and Overton found that a compound's ability to produce narcosis was directly due its partition coefficient, or lipid solubility. Lipnick (1986) published numerous reviews of the historical work of Overton and his extensive and meticulous experiments in which he correlated

solvent narcosis to the oil–water partition coefficient for more than 130 industrial compounds.[73]

Overton's early studies in the late 1800s are particularly relevant because his experimental design involved measuring the oil–water partition coefficient in an aquatic environment with tadpoles and small fish. Compounds that are highly lipid soluble preferentially partition into the fat-rich nervous systems of aquatic animals, causing paralysis. (Lipnick 1989).[74] Overton provided clear evidence of the fate of lipid-soluble compounds and showed they are absorbed by aquatic animals. As previously noted, many of the organic solvents Overton initially tested were chemicals that Monsanto would later show in 1944 (MONS092683)[57] were excellent solvents for PCBs, as described by Lipnick (1986):[73]

> *Overton employed algae and a wide variety of aquatic animals including tadpoles, daphnia, fish, crustaceans, bryozoa, and annelids to study toxicity at a constant blood plasma concentration. Most of the experiments which he reported in detail were conducted using tadpoles of the species* Rana temporia. *The compounds tested included monohydric, dihydric, and polyhydric alcohols, aliphatic and aromatic hydrocarbons, nitriles, nitroparaffins, aldehydes, ketones, sulfones, esters of organic and mineral acids, various aromatic compounds, amines and alkaloids.*

Overton's work not only established that the oil–water partition coefficient was the key property regarding absorption of individual organic compounds, but he also elucidated important toxicokinetic aspects such as the modulating effects of temperature on the time required for absorption of lipophilic compounds. Lipnick (1986) noted:[73]

> *Overton found that within a homologous series, although the partition coefficient continues to increase with chain length, the absolute solubility in oil or a mixture of cholesterol and lecithin at room or blood temperatures decreases rapidly beyond a certain point in the series. For example, phenanthrene, which is readily soluble in olive oil and related substances at room temperature, is a narcotic, but anthracene, an isomer, is not soluble and does not show narcotic effects. Overton concluded that low water*

> *solubility alone will not limit narcotic toxicity, as in the case of phenanthrene which dissolves in about 300 000 to 400 000 parts of water, but produces narcosis at one part in 1500 000. For experiments conducted at this very low concentration, 36 h were required for complete narcosis to take place, which Overton accounted for based upon the slow rate of transport and accumulation of phenanthrene into the ganglia cells.*

Lipnick reproduced Overton's results relating narcosis (bioabsorption) to the olive oil–water partition coefficient in Exhibit 26.[75]

Exhibit 26. Overton's Data on Test Chemicals Producing Complete Narcosis in Tadpoles

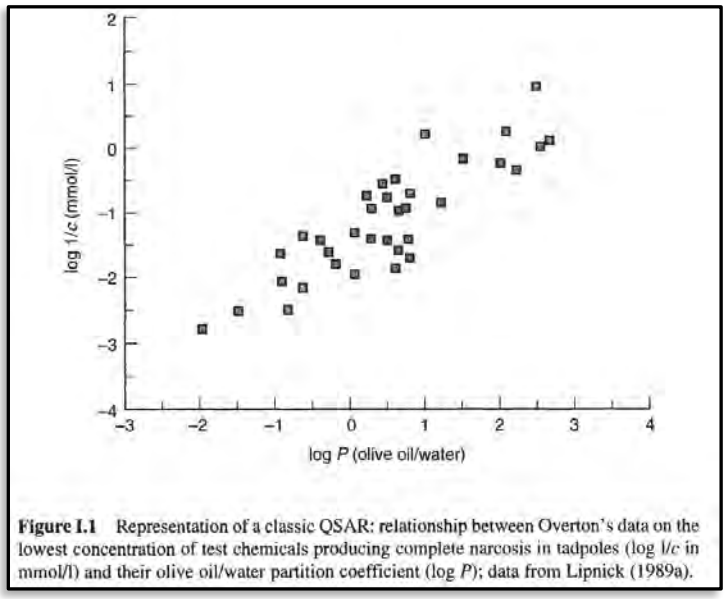


Figure I.1 Representation of a classic QSAR: relationship between Overton's data on the lowest concentration of test chemicals producing complete narcosis in tadpoles (log 1/*c* in mmol/l) and their olive oil/water partition coefficient (log *P*); data from Lipnick (1989a).

Source: Nendza 1998.[75]

Perouansky (2015) also published a retrospective on the scientific achievements of Overton's work and pointed out that Overton published numerous studies that were well known in the scientific community.[59]

Even at this early point, Overton linked the oil–water partition coefficient with the ability of an organic compound to be absorbed through the cell membrane and become embedded or stored in

fat-rich substances. The fatty substances he highlighted were cholesterol, lecithin, and other oily substances that constitute all biological cell membranes, thus explaining why the lipid solubility property of organic compounds is the driving force controlling bioabsorption. Perouansky stated:

> *Overton published five papers between 1895 and 1900 reporting the results of his experiments on the permeability (referred to him, following contemporaneous terminology, as 'osmotic properties') of living plant and animal cells for biological and synthetic substances. In 1899 he expressed his 'suspicion' (note his avoidance of 'hypothesis') that cholesterin or cholesterin-like substances, possibly with lecithin and other oily substances, impregnated the boundary between cell protoplasm and the exterior. This became known as Overton's lipoid theory or 'Overton's rule', which states that the permeability coefficient of a solute is linearly related to its partition coefficient between oil and water. This work has since been celebrated as a foundation stone of membrane science.*

Overton's seminal work in the late 1800s was so important that he is now recognized as laying the foundation for the medical practice of anesthesiology. In his editorial in the *British Journal of Anaesthesia*, Perouansky specifically identified the oil–water partition experiments as a milestone in explaining absorption and bioaccumulation of organic lipophilic compounds:[59]

> *Hardly any discourse on anesthetic mechanisms avoids mention of the Meyer–Overton rule. Thanks to the eponymous rule, Charles Ernst Overton (1865–1933) enjoys together with Hans Horst Meyer (1853–1939) the highest name recognition where anesthetic mechanisms are concerned (Fig. 1). It may therefore come as a surprise, especially for clinicians, that the work underlying Overton's contribution to the Meyer–Overton rule was merely a by-product of Overton's principal body of scientific work; his lifelong interest in the movement of substances between the environment and the interior of living cells.*

Perouansky went further to credit Overton's work, which led to the Overton rule, as contributing to other scientific fields, including toxicology:

> *Overton's work had far-reaching consequences well beyond anaesthesia. It became one of the foundation stones for the conceptualization of the boundary between cell protoplasm and its environment (known today as the cell membrane) and anticipated by several decades the understanding of impulse propagation in excitable membranes. Moreover, his contributions to structure–activity data, to toxicology, and to plant chemistry and genetics are also notable.*

With contributions on the same oil–water partition coefficient phenomenon, another scientist—Hans H. Meyer (1853–1939)—was added to the Overton rule, which is now referred to as the Meyer-Overton rule.[74] This rule is based on the concept that predictions of bioaccumulation can be based solely on how organic industrial compounds partition between oil and water phases, as described by the laboratory measurement of the oil–water partition coefficient. Kurt H. Meyer (Hans Meyer's son) published a study in 1937 that summarized the "lipoid" mechanism, as follows:[76]

> *Any attempt to elucidate the mechanism of narcosis must take account of two well-known facts: firstly, that the same effect is produced by substances belonging to quite different classes of compounds, with a relatively high chemical inactivity as their only common characteristic; and, secondly, that many narcotics leave the body again completely unchanged, without having, on their part, effected any permanent change in it. This leads to the conclusion, first drawn by H. Meyer and Overton, that the action of narcotics depends on the formation of very loose compounds with certain cell constituents; in the opinion of both these workers these constituents were fat-like substances, the "lipoids."*

Meyer discussed how lipophilic compounds interact with lipids in the membrane:

> *There is hardly any other possibility than to take the limiting concentration and to determine, purely physically, the corresponding concentrations set up in various places: at the boundary surfaces, in the albumens, in the fats (triglycerides) and, finally, in the higher alcohols of the fatty series of the cholesterin type. Oleic alcohol was chosen as the model for substances of the latter class, it being the most closely related of all the readily*

> *available substances which might be considered for the purpose. The importance of this relationship cannot be overstated as it is the cornerstone of all fate and transport environmental studies.*

Based on this relationship between the fat-rich membrane and lipid soluble compounds, Meyer stated that the empirical evidence was conclusive:

> *The deduction seems inevitable that such a constant concentration is set up also in the body lipoids, i.e. in the higher alcohols of the organism, and, further, that great biological significance must be attached to this rule. The experimental observation may be formulated as follows: Narcosis commences when any chemically indifferent substance has attained a certain molar concentration in the lipoids of the cell (or, to be more precise in the lipoid alcohols of the cell substance) This concentration depends on the nature of the animal or cell, but is independent of the narcotic. The above statement seems to me to reproduce best the true nature of the Meyer–Overton lipoid theory: it is not really a theory which explains the mechanism of narcosis but rather the expression of an experimentally observed regularity, a rule of which every theory must take account.*

This rule was well-established and used in many scientific disciplines to make predictions about the absorption of lipophilic compounds into terrestrial and aquatic animals by the turn of the 20th century—some 35 years before Monsanto started PCB production.

A competent, independent, academic or industrial scientist working in the early 1900s would have been knowledgeable of the Meyer–Overton rule and would have predicted—on the basis of knowing how lipid-soluble PCBs were—that PCBs were readily absorbed by environmental terrestrial and aquatic animals. A scientist could make such a prediction by knowing that PCBs were extremely lipophilic and were insoluble in water, even in the absence of knowing the specific oil–water partition measured value. As previously noted, determining the oil water partition coefficient of different Aroclors would have been extremely easy and could have been completed in a very short period of time.

By the 1930s, the oil–water partition coefficient was routinely used as the primary tool to investigate the absorption of many different organic industrial compounds. Partition measurements were being used by pharmacologists and toxicologists to predict the absorption of different compounds into fat tissues of biological receptors for the purpose of developing drugs such as anesthetics. The potency of the effect, as well as the toxicity, could then be assessed simply based on a candidate compound being lipophilic. For example, Leake and Chen (1930) used the partition coefficient in pharmacology experiments to identify candidate anesthetic compounds from a family of structurally similar compounds (homologous series).[77] They predicted that increasing the carbon length would increase fat solubility, which would, in turn, increase absorption and ultimately increase toxicity:

> *From a general consideration of the chemo-pharmacological properties of di-ethyl ether and ethylene, especially in regard to their marked anesthetic power and relatively low toxicity, it seemed possible to predict that compounds combining the chemical characteristics of each would be interesting general anesthetic agents. This prediction might be made more specific by further reference to the theory of the relationship between chemical constitution and pharmacological action. In certain homologous series of absorbable aliphatic compounds (as the monohydric alcohols) toxicity increases (without a comparable increase in* desired *activity), in proportion to the number of carbon atoms in the straight carbon chain.*

Exhibit 27 shows the results of the partition coefficient analyses conducted by Leake and Chen for six compounds. This clearly demonstrates that Monsanto could have rapidly and very easily characterized the oil–water partition coefficient for all Aroclor compounds.

Exhibit 27. Leake and Chen: Partition Coefficient Analyses for Six Compounds

TABLE I.
Physico-chemical properties of some unsaturated ethers in comparison with di-ethyl ether.

Substance	Formula	Molecular Weight	Boiling Point	Partition Coefficient, Oil : Water, at 20°C.
Di-ethyl ether	$CH_3—CH_2 \diagdown O \diagup CH_3—CH_2$	74	34.5°C.	2.3±0.1
Vinyl-ethyl ether	$CH_2=CH \diagdown O \diagup CH_3—CH_2$	72	34-36°C.	0.5±0.1
Di-vinyl ether	$CH_2=CH \diagdown O \diagup CH=CH_2$	70	36-39°C.	2.5±0.2
Allyl-ethyl ether	$CH_2=CH—CH_2 \diagdown O \diagup CH_3—CH_2$	86	68-74°C.	2.0 †
Isopropenyl-ethyl ether	$CH_2= C(CH_3) \diagdown O \diagup CH_3—CH_2$	86	59-63°C.	0.61±0.1
Di-allyl ether	$CH_2=CH—CH_2 \diagdown O \diagup CH_2—CH=CH_2$	98	92-98°C.	2.0 †

Source: Leake and Chen 1930.[77]

Hans Meyer's 1937 study extended the previous investigations on the importance of the oil–water partition coefficient in making predictions about bioaccumulation.[76] He showed that compounds with quite different chemical structures, but similar oil–water partition coefficients, are similarly absorbed.

A year after Meyer published his work, chemical industry scientists involved in the production of chlorinated compounds at chemical companies were using oil–water partition coefficients to classify industrial chemicals. For example, Ferguson (1938), who was a toxicologist at Castner-Kellner Alkali Company (which, like Monsanto, produced chlorinated organic compounds) published a treatise on the mechanisms of toxicity, stating [78]

> *A number of investigations have been published in which attempts are made to correlate the chemical or physical properties of substances with the intensity of their toxic action.*

Ferguson noted that, by this time, it was clear the physicochemical oil–water partition coefficient property governed absorption across the fat rich membrane and bioaccumulation for diverse lipophilic chemicals. He, like Meyer,[76] showed that diverse substances with the same lipid solubility will be absorbed similarly:[78]

> *The great influence of phase distribution relationships in determining the values of physiologically active concentrations if of course recognized in the Meyer-Overton lipoid theory of narcosis. In the later form of this theory adopted by K. H. Meyer (Meyer and Hemmi 1935), it is assumed that isonarcotic effects are produced by the most diverse substances when their molar concentrations in the cell lipoids are identical.*

He also noted that other studies were being published to correlate their physical properties with their toxic action.

> *A number of investigations have been published in which attempts are made to correlate the chemical or physical properties of substances with the intensity of their toxic action.*

Ferguson was interested in extending Meyer's lipoid studies to correlate other chemical and physical properties of industrial chemicals and develop a rule for classification. Clearly, the oil–water partition coefficient properties of organic compounds was extending to toxicology and the chemical industry solely based on the property of lipid solubility.

By 1943, occupational physicians were warning their colleages not to ignore the physical properties of industrial compounds with regard to the lipid solubility. For example, Dr. Goldblatt, of Imperial Chemical Industries (a large British industrial chemical company), delivered a lecture to the Association of Industrial Medical Officers in October of 1943 warning that lipid-soluble compounds could be absorbed into the body and pose a health threat to workers.[79] He stated:

> *The purpose of this paper is to draw the attention of medical officers in industry who are responsible for the health of workers engaged in operations involving the use or*

> *manufacture of toxic materials, to the importance of a measure of fundamental or elementary knowledge of the measures that must be taken to discover the dangerous properties of such materials.*

Goldblatt urged his fellow physicians to focus on the physical properties of the diverse industrial compounds in order to identify those compounds with high lipoid solubility because they are absorbed through the skin, which can produce toxic effects:

> *In the vast field of organic compounds, there is a tendency to ignore purely physical properties, particularly when dealing with solids. I always look with suspicion at materials of low melting point and high or considerable lipoid solubility if in association with toxic radicles. These are the compounds which more or less readily penetrate the skin. In general, these compounds show little, if any, solubility in water.*

Notably, Goldblatt expressed concern that lipophilic compounds pose a specific risk relating to lipid solubility. The emphasis had shifted from the toxic effects on the skin itself (like chloracne) to the bioabsorption through the skin that could lead to bioaccumulation in the body. That is, skin was not the target but was a route of bioabsorption and entry into the bloodstream, where the chemical could then attack target organs:

> *No discussion of industrial hazards can overlook reference to the skin. As an industrial route of entry of toxic products into the organism, the skin is second only to the lungs. Reference has been made to the rough general criteria of skin absorbability—viz. low melting point, lipoid solubility or miscibility, fat solvents.*

By 1944, the oil–water partition coefficient was used as the basis for classifying chemical toxicity in industrial medicine and hygiene programs. For example, Lazarev (Lipnick and Filov 1992) used this sole physicochemical property to classify lipid-soluble organic compounds that were bioaccumulative and could cause toxic effects in workers.[80] Recognizing that many toxic industrial compounds were lipid soluble, Lazarev developed a framework based on the oil–water partition coefficient in a series of industrial hygiene studies in which he calculated the Kow for

each compound. Lipnick and Filov noted that Lazarev called lipophilic compounds "nonelectrolytes" (they have limited solubility in water and are not charged molecules) and published a compendium of his work:

> *In his 1944 monograph* Neelektrolity' (Nonelectrolytes) *(Fig. l), Russian scientist Nikolai Vasilyevich Lazarev proposed a system for the biological, physical and chemical characterization of nonelectrolytes, using the logarithm of the olive oil/water partition coefficient (log Koil/water) as a primary measure of classification. This system provided a framework for developing a systematic approach to toxicology that was needed to set industrial hygiene standards for workplace exposure to organic chemicals in the Soviet Union.*

Lipnick and Filov prepared a table from Lazarev's work that shows numerous toxic effects are associated with an increase in the lipid solubility (partition coefficient) (Exhibit 28). It is particularly noteworthy that, as demonstrated by the previous studies by Overton and Meyer, scientists knew at this point in time that, with an increase in the partition coefficient, lipid-soluble chemicals bioaccumulate in both aquatic receptors and humans. That is, lipid-soluble industrial compounds could be predicted to accumulate in environmental and human receptors as they partitioned into fat-rich organs.

Exhibit 28. Lazarev's Increasing Partition Coefficient Correlations

Table 1. Correlations of Lazarev with increasing partition coefficient or decreasing water solubility. (Adapted from [23].)

Effect	Subject
Increase in degree of irritancy of organic liquids	Skin
Increase in degree of reversible aggregation of liquid particles	Coacervate emulsion (phospholipid and oleate)
Decrease in concentration needed to produce a 6% reduction in staining	Fixed frog gastrocnemius
Decrease in concentration needed	*In vitro* hemolysis
Decrease in concentration required	50% Reduction of bird erythrocyte respiration
Decrease in concentration	Arrest of isolated frog heart
Decrease in minimum concentration	Contraction changes in isolated segments from heart ventricle
Decrease in concentration	Paralyzing action on isolated rabbit intestine
Decrease in concentration	Narcosis in tadpoles and small fish
Decrease in concentration in blood of mammals	Change in reflex time, narcosis, respiratory failure, or death
Decrease in blood concentration	Respiratory failure in frog
Decrease in concentration	Irritation of the eye or tongue
Decrease in concentration	Anesthesia via intradermal administration

Source: Lipnick and Filov 1992.[80]

Lipnick and Filov noted that Lazarev's industrial hygiene study built on the historical work started by the Meyer and Overton studies more than four decades earlier. Lazarev recognized the overwhelming complexity of evaluating each of the vast number and chemically diverse industrial chemicals to characterize the myriad toxicokinetic parameters (absorption, distribution, metabolism, and excretion [ADME]). As this would have been a Herculean task, Lazarev simplified the analysis of industrial compounds by exclusively focusing on lipid solubility using the Know (Exhibit 29):

> *Given this complexity, he sought to derive regular relationships between chemical structure and physicochemical properties that could be used in relating chemical structure to biological activity. Although Lazarev considered studying various homologous series of compounds, he concluded that this approach was not practical due to the infinite number of such series. Instead, he chose as his starting point Richet's 1893 report of an inverse relationship between water solubility and narcotic effect on small*

fish, and the broader and more precise independent studies of Meyer and Overton relating partition coefficient to narcotic potency.

As noted in the previous discussions, this is the identical scientific approach that is still used today by U.S. and E.U. regulators to predict which industrial organic compounds will bioaccumulate in order to prevent worldwide pollution from organic compounds such as PCBs, which were historically released into the environment in massive quantities.

Exhibit 29. Lazarev's Kow Equations: Physicochemical Properties, In Vitro Effects, and In Vivo Effects

TABLE II. Equations derived by Lazarev relating partition coefficient or water solubility of nonelectrolytes to their other properties

Physicochemical properties

$\log K_{benzene/water} = 1.05 \log K_{oil/water} + 0.32$

$\log S = -0.89 \log K_{oil/water} + 3.15$

***In vitro* effects**

$\log C_{hemolysis} = -0.62 \log K_{oil/water} + 2.45$

$\log C_{hemolysis} = 0.73 \log S + 0.10$

$\log C_{bird\ erythrocyte\ respiration} = -0.72 \log K_{oil/water} + 2.05$

$\log C_{bird\ erythrocyte\ respiration} = 0.74 \log S - 0.20$

***In vivo* effects**

$\log C_{tadpole\ narcosis} = -0.69 \log K_{oil/water} + 1.06$

$\log C_{tadpole\ narcosis} = 0.72 \log S - 1.04$

$\log C_{ocular\ irritation} = 0.72 \log S - 0.60$

From Ref. 1.

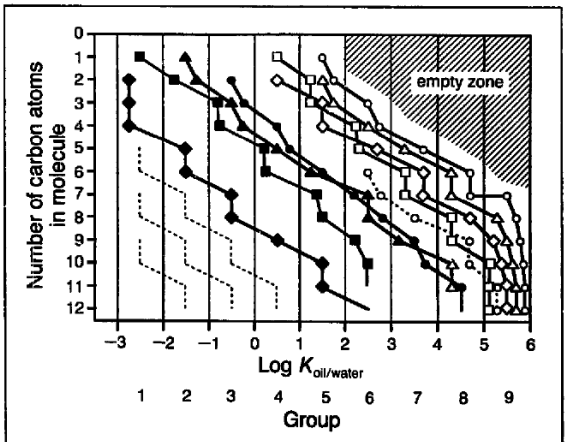


Fig. 3. Effect of increasing number of carbon atoms within homologous series on Lazarev's group number and of the olive oil/water partition coefficient. (○–○) alkanes; (△) alkenes; (□) alkynes; (◇) phenyl-substituted; (○- - -○) monochloro-substituted; (●) saturated esters of fatty acids; (▲) primary unbranched monohydric alcohols; (■) saturated fatty acids; (◆) saturated dibasic acids. Adapted from Fig. 4, Ref. 1.

Source: Lipnick and Filov 1992.[80]

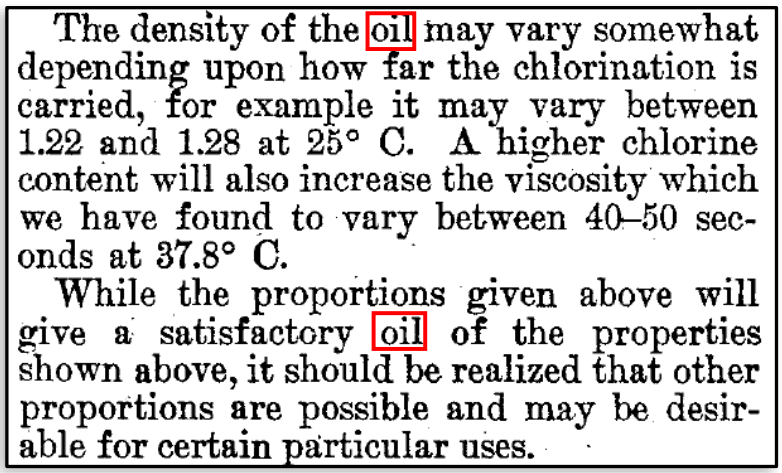
6.3. Monsanto Must Have Known that PCBs Were Highly Lipophilic Oils, and Would Bioaccumulate, as Early as 1929

This section provides evidence that Monsanto must have known PCBs were lipid soluble the entire time it manufactured PCBs, such that Monsanto must have known that PCBs would bioaccumulate.

PCBs were initially produced by the Swann Research, Inc., starting in 1929, when a patent application for producing an "insulating di-electric liquid" adapted "to be used as a filling material for oil immersed transformers" was submitted by C. McCullough, et al., of the Swann company.[69] From this very quote, Swann (later acquired by Monsanto) knew PCBs were lipid soluble and even labeled them "oils" in the patent application.

As its patent application (Exhibit 30), Swann consistently referred to "chlorinated diphenyls" (as they were called then, rather than biphenyls or PCBs) as "oils:"

Exhibit 30. Excerpt from Swann Research, Inc., PCB Patent Application, 1929



The density of the oil may vary somewhat depending upon how far the chlorination is carried, for example it may vary between 1.22 and 1.28 at 25° C. A higher chlorine content will also increase the viscosity which we have found to vary between 40–50 seconds at 37.8° C.

While the proportions given above will give a satisfactory oil of the properties shown above, it should be realized that other proportions are possible and may be desirable for certain particular uses.

Source: https://patents.google.com/patent/US1836180A/en

From this patent, it is clear that Swann/Monsanto knew PCBs were oils and were, therefore, lipophilic.

The next year (1930), Penning (who worked at Swann company) published a study detailing many of the physicochemical properties of PCBs.[81] One of the properties of these newly produced Aroclors that he emphasized was that they were lipid soluble and were miscible (dissolved) in "a large number of organic liquids" (as only lipophilic compounds are):

> *This mixture, being liquid through a wide temperature range, exhibits marked solvent properties, and is itself soluble in or miscible with a large number of organic liquids.*

According to Penning, the Aroclor oils were stable (which led to their persistence because they do not undergo oxidation) and remained fluid oils that were thermoplastic (they do not change their physical state, which is an oil):

> *The Aroclor oils are non-drying; they undergo no appreciable oxidation or hardening on exposure to air. Similarly, the Aroclor resins are apparently permanently thermoplastic. They undergo no further condensation or hardening on repeated melting and cooling, so far as experiments have been carried.*

Even in 1930, PCBs were known to be insoluble in water but soluble in a "wide range of other liquids, including practically all of the ordinary organic solvents," as well as mineral and vegetable oils. This was not surprising, since all scientists had known since the 15th century that likes dissolve likes:

> *The Aroclors are insoluble in water; they are also insoluble in glycerol, and not readily soluble (particularly those of high chlorine content) in the lower alcohols, but they are soluble in a very wide range of other liqids, including practically all of the ordinary organic solvents, solvent mixtures, and mineral and vegetable oils.*

Exhibit 31 shows that Aroclors 1242 and 1254 were liquid oils at normal room temperature, while other terphenyls and higher chlorinated Aroclors were waxy resins (that become oils upon heating):

Exhibit 31. Physical Characteristics of Chlorinated Diphenyls

Table I—Physical Data on Chlorinated Diphenyls

Property	Technical Diphenyl	Aroclor 1219	Aroclor 1242	Aroclor 1254	Aroclor 1262	Aroclor 1268	Aroclor 2565	Aroclor 4465
Appearance	Very light yellow crystals	Water-white liquid	Water-white liquid	Pale yellow liquid	Light yellow, waxy resin	Pale yellow, hard, crystalline mass	Black resin	Pale amber resin
Melting or softening point	68.6° C.	14° C.	Liquid at 0° C.	Pliable wax at 0° C.	Brittle resin at 0° C.	127–171° C.	78° C.	70° C.
Boiling point or distillation range	255.6°	278–295° C.	320–360° C.	360–400° C.	374–410° C.	395–415° C.	250–360° C. (10 mm.)	240–290° C. (9 mm.)
Specific gravity	1.007	1.1567 (25°/25° C.)	1.36 (65°/65° C.)	1.52 (65°/65° C.)	1.64 (65°/65° C.)	1.8 (65°/65° C.)	1.7 (25°/25° C.)	1.7 (25°/25° C.)
Viscosity, seconds Saybolt at 210° F.		30	34	46	96	Solid	Solid	Solid
Flash point	118–119° C.	127° C.	174–178° C.	210° C.	221° C.	241°	230°	257°
Flame point	139–143° C.	176° C.	224° C.	None below boiling	None below boiling	None up to 405° C.	None up to 405° C.	492° C.
Refractive index		1.6125	1.6248	1.6391	1.6493			

Source: Penning 1930.[81]

It is also interesting to note that, from the very beginning, PCBs were promoted as additives to surface coatings like varnishes, lacquers, and plastic resins because they were oily compounds and would, therefore, serve to prevent cracking, whereas coatings without the oily PCBs could become brittle. Penning described this as follows:

> *PROTECTIVE COATINGS—The protective-coating industries are greatly interested in Aroclor, and a large amount of work is being done in this line. Quick-drying tung oil varnishes have been made with both the viscous (Aroclor 1254) and the resinous (Aroclor 4465) Aroclors, and the solubility of the viscous products in linseed and tung oils indicates their use as plastic resins or gums for varnishes, especially of the short oil type where failure is due to cracking of a brittle resin present.*

Penning also highlighted numerous other applications of PCBs that were being suggested by customers that could be used at reasonable prices:

> *MISCELLANEOUS USES—Printing inks, artificial leather, leather finishing, textile finishing—no attempt will be made to complete the list of multitudinous projects on which*

> *work is being done with the Aroclors. And when it is considered that these products represent only one of the many types of derivatives which may be made from diphenyl, one gets some idea of the enormous field opened by the production of this compound at a reasonable price.*

Monsanto took advantage of the oil–water partition coefficient of PCBs in a 1944 patent application by Paul Benignus (a Monsanto employee).[82] In this patent, a new fungicide application was developed based on PCBs being insoluble in water but soluble in oils (meaning they would have a high oil–water partition coefficient). These oil–water emulsions (emulsions refer to a fine dispersion of minute droplets of oil suspended in water, as they are immiscible) were necessary because salts (which imparted the fumigant property) do not dissolve in PCBs, making the addition of water necessary to dissolve the salts.

> *One of the objects of the present invention is to provide a process whereby textiles, cordage, paper, wood and other cellulosic or part cellulosic materials may be impregnated with sufficient amount of relatively insoluble fungicidal agents in a single immersion to render the subsequently dried cellulosic material permanently and effectively resistant to the action of fungus and bacteria.*

This fungicide emulsion was developed specifically for application to "textiles, cordage, paper, wood and other cellulosic or part cellulosic materials." Uses of the treated fabrics and textiles were not specified, but it appears that any material used outside that could become wet and encourage fungal growth were potential materials for treatment. They were also materials that needed to be laundered or washed at some point with soap and water because Monsanto tested them under those conditions.

Ultimately, the goal of the PCB oil–water emulsion was clear: to make the coating "permanent" and water resistant. This new PCB-emulsion application would replace the water-soluble fumigant formulations used at the time that were removed with washing. Thus, Monsanto not only knew PCB had a very high oil–water partition property, but the company capitalized on this

specific property of PCBs to develop this new PCB-emulsion application. Benignus emphasized these properties: [82]

> *However, subsequent wetting or laundering of the fabric thus treated tends to remove the fungicidal or bactericidal agent and thereby to reduce drastically the resistance of the fabric to fungi and bacteria.*

The PCB-emulsion was prepared in a range of water phase to oil phase ratios, but a 1:1 ratio of oil–water was recommended:

> *The emulsion composition of the present invention may contain any desired proportions of water phase to oil phase in the range of 1:4 to 4:1. A desirable proportion is that of 50 parts of water and 50 parts of oil.*

The proportion of PCBs in the emulsion could exceed 25% of the total volume:

> *The quantity of chlorinated diphenyl mixture which may be employed in the composition may be varied over a wide range, for example, from 3% or less to 25% or more.*

Monsanto clearly identified the entire range of Aroclors that were amenable to this oil–water emulsion as it states that Aroclor 1242, 1254, and 1260 could be used:

> *The chlorinated diphenyls suitable as components of the composition of this invention are the mixtures of chlorinated diphenyls obtained by chlorinating diphenyl and which mixtures contain from 20–68% of chlorine.*

It is interesting to note that Monsanto claimed that this new PCB-based oil–water emulsion would perform as advertised because the conducted tests to show the PCBs were not removed after the fabrics were laundered. In these tests, Monsanto treated “a cotton duck fabric” and washed it for 40 minutes at 100 degrees Celsius, and the PCB emulsion remained bound to the material and was not significantly altered:

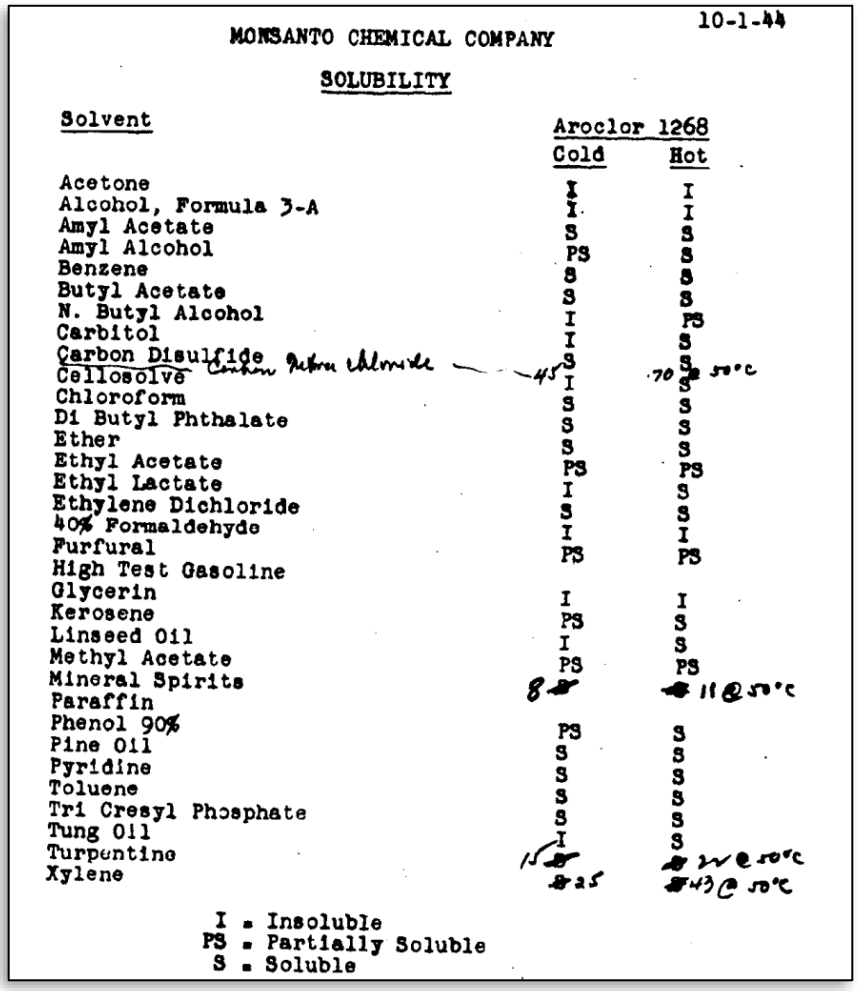
> *A cotton duck fabric was impregnated with the emulsion in a vessel equipped with squeeze rolls and known in the art as a padder. Following the impregnation, the fabric was air dried. A portion of the treated fabric was laundered for 40 minutes at 100° C with hot soap water, rinsed four times with water and air dried. The laundering procedure thus employed was that known as the standard cotton wash test of the American Association of textile Chemists and Colorists.*

In addition to the patents, Monsanto also produced numerous sales brochures for its salesmen to share with potential customers, highlighting diverse physicochemical properties of PCBs, including that PCBs were highly soluble in a wide range of organic fat-soluble solvents, they were not soluble in water, and they were highly resistant to degradation. For example, a 1944 Monsanto Chemical Company "Salesmen's Manual" for Aroclors (MONS092683) stated that they were mixtures of compounds based on "physical properties" rather than on "chemical composition."[57]

> *DESCRIPTION AND PROPERTIES*
>
> *The Aroclors are a series of chlorinated hydrocarbons based on biphenyl and terphenyl. They are not pure compounds but are mixtures of closely related chlorine substitution products manufactured essentially to a set of specifications based on physical properties rather than chemical composition.*

Another page from this manual touts the number of organic solvents with which PCB was miscible (Exhibit 32). Being soluble in a wide variety of industrial organic solvents like benzene, toluene, and xylene created sales opportunities for PCBs. This highlights the fact that Monsanto clearly knew PCBs were lipid soluble because only lipophilic compounds are miscible with organic solvents. These were all organic solvents that were used industry-wide to dissolve oils, fats, and other lipophilic compounds the chemical industry was manufacturing.

Exhibit 32. Excerpt from Monsanto Chemical Company's Salesmen's Manual: Solubility of Aroclor 1268



MONSANTO CHEMICAL COMPANY 10-1-44

SOLUBILITY

Solvent	Aroclor 1268 Cold	Aroclor 1268 Hot
Acetone	I	I
Alcohol, Formula 3-A	I	I
Amyl Acetate	S	S
Amyl Alcohol	PS	S
Benzene	S	S
Butyl Acetate	S	S
N. Butyl Alcohol	I	PS
Carbitol	I	S
Carbon Disulfide	S	S
Cellosolve	I	S
Chloroform	S	S
Di Butyl Phthalate	S	S
Ether	S	S
Ethyl Acetate	PS	PS
Ethyl Lactate	I	S
Ethylene Dichloride	S	S
40% Formaldehyde	I	I
Furfural	PS	PS
High Test Gasoline		
Glycerin	I	I
Kerosene	PS	S
Linseed Oil	I	S
Methyl Acetate	PS	PS
Mineral Spirits		
Paraffin		
Phenol 90%	PS	S
Pine Oil	S	S
Pyridine	S	S
Toluene	S	S
Tri Cresyl Phosphate	S	S
Tung Oil	I	S
Turpentine		
Xylene		

I = Insoluble
PS = Partially Soluble
S = Soluble

Source: Monsanto Chemical Company's Salesmen's Manual 1944.[57]

PCBs were widely known in the scientific community to be lipid soluble. In his comprehensive toxicity study of Aroclor 1242, Miller emphasized that PCBs were insoluble in water but soluble in vegetable oils and "fat solvents":[17]

> *The chlorinated diphenyl used was viscous, almost water white, and clear at room temperature. It consisted of a mixture of isomers of diphenyl chlorinated in different positions and extent, with an approximate chlorine content of 42 percent and an*

approximate empirical formula of $C_{12}H_7Cl_3$. It was insoluble in water but soluble in mineral and vegetable oils, other chlorinated hydrocarbons, and fat solvents. Its specific gravity was 1.374 to 1.393.

7. MONSANTO KNEW IN 1935 THAT PCBS WERE STABLE AND PERSISTENT LIPOPHILIC COMPOUNDS.

In addition to its very high lipid solubility, Monsanto documents demonstrate an understanding of PCBs' stability. In fact, Monsanto referred to PCBs as stable compounds that resist degradation. This is the characteristic that lead to PCBs becoming a ubiquitous and worldwide environmental contaminant. Although the first study into the widespread environmental pollution of PCBs was triggered by Soren Jensen's (1966) work on this topic, Monsanto should have predicted and foreseen this result from the earliest chemical analyses of PCBs Because the chemical structure of PCBs had been known since its synthesis in the 1800s.[50]

As an example of Monsanto's knowledge of PCBs resistance to chemical breakdown (which was used in sales pitch to potential customers), it prepared a 1944 sales brochure (MONS092683) to tout the chemical stability of the PCB molecule. [57] Monsanto claimed in this brochure titled, "Salesmen's Manual: Aroclor Description and Properties" that one of the most "outstanding" physicochemical properties of Aroclors was its resistance to degradation from light, water, acids and alkalies, oxidation, and chemical action. The company was correct in 1944 to make such a statement. However, while the chemical stability of PCBs was widely recognized by Monsanto as a "virtue," serving as a sales pitch for Monsanto's Aroclors, the fact that they do not break down when released into the environment and can survive harsh environmental conditions cause the chemicals to be persistent in the environment.

In Monsanto's tests to determine PCBs' compatibility with different metals, Monsanto (MONS092683) showed that while there was some interaction with copper, it found no evidence of dechlorination from the biphenyl rings:[57]

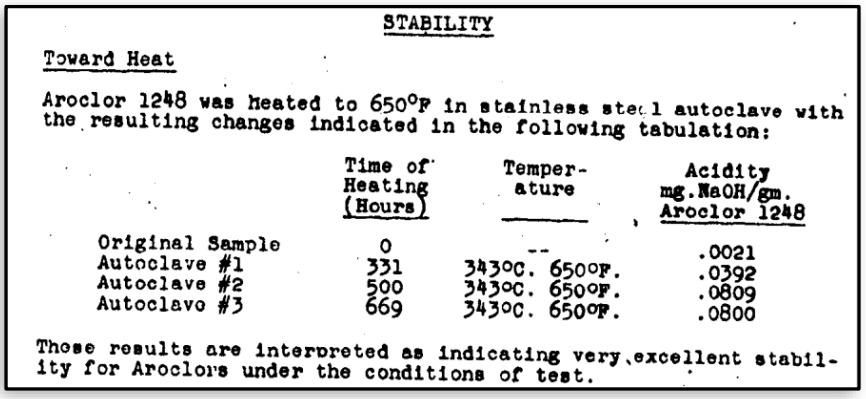
Toward Oxidation

When Aroclor 1254 is heated for 50 or 0 days at 150°C in the presence of oxygen and copper, there is likely to be some attack on the copper. Examination of Aroclor 1254 after that period of time will usually show the presence of soluble copper. This also occurs with mineral oil and other insulating liquids.

In general, even after severe oxidation conditions no evidence of chlorine splitting from the parent hydrocarbon has been found [emphasis added].

Likewise, PCBs were extremely resistant to degradation with high heat, as shown in Exhibit 33.

Exhibit 33. Excerpt from Monsanto Chemical Company's Salesmen's Manual: Stability of Aroclor 1248



STABILITY

Toward Heat

Aroclor 1248 was heated to 650°F in stainless steel autoclave with the resulting changes indicated in the following tabulation:

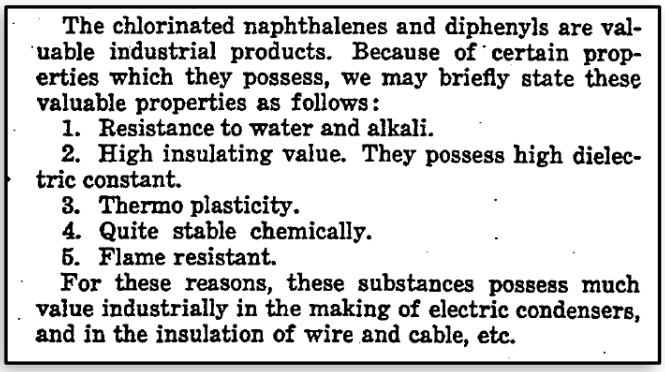
	Time of Heating (Hours)	Temperature	Acidity mg.NaOH/gm. Aroclor 1248
Original Sample	0	--	.0021
Autoclave #1	331	343°C. 650°F.	.0392
Autoclave #2	500	343°C. 650°F.	.0809
Autoclave #3	669	343°C. 650°F.	.0800

These results are interpreted as indicating very excellent stability for Aroclors under the conditions of test.

Source: Monsanto Chemical Company's Salesmen's Manual 1944 (MONS092683).[57]

Monsanto summarized the stability of PCBs by noting four "valuable" properties, as seen in Exhibit 34.

Exhibit 34. Excerpt from Monsanto Chemical Company's Salesmen's Manual: Valuable Properties of Chlorinated Naphthalenes and Diphenyls



The chlorinated naphthalenes and diphenyls are valuable industrial products. Because of certain properties which they possess, we may briefly state these valuable properties as follows:

1. Resistance to water and alkali.
2. High insulating value. They possess high dielectric constant.
3. Thermo plasticity.
4. Quite stable chemically.
5. Flame resistant.

For these reasons, these substances possess much value industrially in the making of electric condensers, and in the insulation of wire and cable, etc.

Source: Monsanto Chemical Company's Salesmen's Manual 1944 (MONS092683).[57]

In another 1948 Monsanto Technical Bulletin (MONS 074287),[83] Monsanto extolled the fact that Aroclor 1254 was very persistent because it was resistant to degradation from "biological influences" and attacks by bacteria. This property is extremely important, because microbial degradation is one of the most efficient processes for degradation of industrial chemical compounds. In fact, many polluted sites rely on microbial degradation as a remedy selected for cleanup.

Statements that none of the known physical mechanisms for degrading chemicals would work on PCBs, and that PCBs do not undergo microbial degradation, indicate an understanding of PCBs' stability and persistence. From as early as 1948, Monsanto's documents extoll PCBs' resistance to microbial degradation:

> *VIII. ADVANTAGES OF USING AROCLOR 1254 IN COMBINATION WITH DOP (a coplasticizer)*
>
> 1. *Depending on the plasticizer ratios used as indicated above, it is possible to save from $1 to $2 per cubic foot of plastic.*

2. *Aroclor 1254 offers superior pigment grinding and pigment dispersing qualities in preparing the organosol.*
3. *The use of Aroclor 1254 in these plastics markedly reduces their susceptibility to burning.*
4. *Aroclor offers outstanding electrical properties and resistance to organism attack.*
5. *Aroclor offers toughness and tensile strength and in other respects the over-all qualities of the plastic such as "hand", flexibility and gloss are maintained.*
6. *Aroclor 1254 resists attack by biological influences.*

Most organic compounds breakdown and are detoxified in the environment by microbial degradation. Not only were PCBs highly resistant to "microorganism attack" but Monsanto believed that PCBs could actually kill microorganisms (PCB-ARCH0232927). In a 1948 letter to Dr. Leake of the U.S. Department of Agriculture (MONS 1987737), Dr. Benignus stated that work had been ongoing to evaluate Aroclor 1242 as a pesticide (miticides, larvicides, and mosquito repellents):[84]

> *During a recent trip to Washington, we had opportunity to discuss with Dr. E.E. Knipling the work done with Aroclors at Orlando, Florida, as lousicides, miticides, larvicides and mosquito repellents given in the USDA Report E-733.*

and

> *Although the biphenyl Aroclors, and especially the lower chlorinated members of the series are known to possess activity as lousicides, miticides, larvicides and show synergistic action on nicotine, these properties seem to diminish with higher chlorination…*

In addition, Monsanto was in the process of determining the solubility of Aroclors in DDT and even provided PCBs to the Department of Agriculture so the agency could perform its own tests.

> *In accordance with Dr. Knipling's suggestions, we are sending you without charge one gallon each of Aroclors 1221, 1232, 1242 and 1248 and also one gallon of MB-40. Our laboratory is scheduled to determine the solubility of DDT in the various Aroclors and also check the similar solubility in MB-40. It is our understanding that MB-40 will dissolve about 20 percent by weight of DDT. MB-40 is considered to be relatively non-phytotoxic.*

In a 1950 Monsanto Technical Bulletin (PCB-ARCH-EXT0020686), Monsanto again highlighted the fact that Aroclors could kill soil microbes—the very microbes that were responsible for PCB degradation—even labeling them as "soil-poisons."[85]

> *AROCLORS* USED IN COMBINATION WITH SANTOPHEN* 20 (PENTACHLOROPHENOL TECHNICAL) IN THE PREPARATION OF WOOD-TREATING FORMULATIONS AND SOIL-POISONS*

In addition to insecticidal properties, Monsanto must have conducted tests to ensure PCBs were stable in soil, since PCBs would not have commercial value as pesticides if they underwent environmental degradation:

> *Liquid Aroclors such as Aroclor 1242 are highly efficient soil-poisoning agents used to treat soil to protect wood against attack by termites.*

In a 1953 technical bulletin (TOWOLDMON0037820), Monsanto promoted the use of Aroclors as pesticide "extenders" to be mixed with Lindane (a pesticide):[86]

> *Synergism, however, cannot be readily predicted and the possibility of synergism in this Aroclor-lindane mixture is at the present time being investigated by the Bureau of Entomology and Plant Quarantine.*

Although the document primarily referred to Aroclor 5460 (which is a terphenyl), it does mention using Aroclors 1254, 1260, and 1268.

In 1961, Monsanto explicitly promoted the fact that Aroclors were "just about the most unreactive materials ever synthesized" and resistant to degradation in an advertisement in *Chemical & Engineering News* (PCB-ARCH0232927).[87] The blaring heading stated:

"THE UBIQUITOUS AROCLOR "GENIE" DOES IT AGAIN!
SECRET OF THE SORCERY?"

Monsanto claimed that Aroclors were just about the most "*un*reactive materials ever synthesized." According to Monsanto, they "stubbornly refuse to volatilize, oxidize, hydrolyze, harden, disintegrate, burn, condense, or corrode anything!"

8. MONSANTO MUST HAVE KNOWN BY 1945-1950 THAT PCBS BIOACCUMULATE AND BIOMAGNIFY.

This section will show that, by 1945-1950, Monsanto must have known that PCBs would bioaccumulate in the environment given 1) the chemical's similarity to DDT and 2) knowledge in the scientific industry that DDT bioaccumulated and biomagnified in the food web.

Between 1945 and 1950, an explosion of peer-reviewed scientific studies provided definitive proof that a highly lipophilic and persistent chlorinated organic compound (DDT) would bioaccumulate and biomagnify in the food web. From the start, all DDT investigations singled out lipid solubility as the one property responsible for DDT bioaccumulation and biomagnification. By 1944, Monsanto was producing both DDT and PCBs;[88] both chemicals have very similar chemical structures and nearly the same lipid solubility. Based on my research, the entire scientific and regulatory community was keenly aware of DDT's ability to bioaccumulate and biomagnify based on its lipid or fat solubility (Woodard 1945; Bishopp 1946).[89], [90] Given that PCBs have similar chemical structures and nearly identical lipid solubility, Monsanto must have known that PCBs would bioaccumulate and biomagnify if released into the environment. Given that PCBs have similar chemical structures and nearly

identical lipid solubility, Monsanto must have known that PCBs would bioaccumulate and biomagnify if released into the environment.

As discussed in the previous sections, the lipid solubility of PCBs was the only physicochemical laboratory information that would have been necessary for Monsanto to predict the bioaccumulation of PCBs into animals and humans, and as discussed above, Monsanto must have been aware by 1935 that PCBs were lipid soluble.

Starting in 1944, new and empirical information was published in the major peer-reviewed scientific journals proving that a lipophilic compound would bioaccumulate and *biomagnify*. These studies analyzed DDT.

By about 1950, the amassed published studies left no doubt in the scientific and regulatory communities that DDT was highly bioaccumulative and biomagnified in the food web. Even the earliest studies proved this fact; by around 1946, when the question of bioaccumulation was definitively answered, attention focused on how far up and how fast DDT traveled up the food chain. With the alarming answer that DDT could easily biomagnify between species by 10- or 100-fold and very rapidly contaminate the entire food web, the questions very quickly moved to human exposures and health. The questions of whether DDT was absorbed through the placenta to expose the human fetus and whether it was secreted into breast milk were also answered in a quick succession of studies. Science is typically cautious, methodical, and slow, but the answers to all these questions regarding DDT were answered almost immediately in by 1950. Afterword, there were few remaining questions regarding bioavailability and biomagnification. Next scientific investigation turned to determining the toxic effects associated with the inexorably bioaccumulated DDT in humans and the U.S. food supply. In this section, I summarize the most salient aspects of the published research dealing with bioaccumulation and biomagnification during 1945–1950. Given the similarities between DDT and PCBs, the industry-wide knowledge of DDT bioaccumulating and biomagnifying, and the fact that Monsanto manufactured DDT, Monsanto must have known by 1945-1950 that PCBs would bioaccumulate and biomagnify if released into the environment.

DDT was first synthesized in 1874, but its effectiveness as an insecticide was only discovered in 1939. Shortly thereafter, and particularly during World War II, chemical companies in the United States began producing massive quantities of DDT to control insects that were responsible for a wide variety of vector-borne diseases such as typhus and malaria in order to protect U.S. troops fighting abroad. After 1944, DDT production shifted to widespread commercial use, and massive amounts of DDT were intentionally released into the environment to kill insects. Although DDT was assumed to be safe during wartime exposure, the Department of Defense conducted no studies related to the impacts of DDT on the environment or food web, or any short-term or chronic toxicity studies. Determinations regarding the toxicity and safety of DDT were largely based on a few acute lethality studies. It was only after 1944-1945 when commercial production began in earnest for several chemical companies (as noted previously Monsanto's production began in 1944), that numerous scientific studies were launched. These studies focused on the impacts of DDT on the environment, environmental terrestrial and aquatic receptors, livestock, and the food supply, as well as human exposures.

Massive quantities of DDT were released into the environment from 1945 to 1972. EPA states:[91]

> *After 1945, agricultural and commercial usage of DDT became widespread in the U.S. The early popularity of DDT, a member of the chlorinated hydrocarbon group, was due to its reasonable cost, effectiveness, persistence, and versatility. During the 30 years prior to its cancellation, a total of approximately 1,350,000,000 pounds of DDT was used domestically.*

Although it is widely assumed that Rachel Carson's book *Silent Spring* started the push to ban DDT, that effort started more than a decade before. In the late 1950s, regulatory action was initiated to limit environmental uses; by 1972, DDT was banned. The EPA provides a brief summary of DDT's historical use and ultimate ban:[92]

> *The U.S. Department of Agriculture, the federal agency with responsibility for regulating pesticides before the formation of the U.S. Environmental Protection Agency in 1970,*

began regulatory actions in the late 1950s and 1960s to prohibit many of DDT's uses because of mounting evidence of the pesticide's declining benefits and environmental and toxicological effects. The publication in 1962 of Rachel Carson's Silent Spring *stimulated widespread public concern over the dangers of improper pesticide use and the need for better pesticide controls.*

In 1972, EPA issued a cancellation order for DDT based on its adverse environmental effects, such as those to wildlife, as well as its potential human health risks. Since then, studies have continued, and a relationship between DDT exposure and reproductive effects in humans is suspected, based on studies in animals. In addition, some animals exposed to DDT in studies developed liver tumors. As a result, today, DDT is classified as a probable human carcinogen by U.S. and international authorities.

EPA provides a short chronological summary of the regulatory action milestones taken as early as 1957 to protect "aquatic areas:"

Initial Federal Regulatory Actions

The Federal Government has not been oblivious to the hazards of DDT use as is indicated by various Government studies and actions undertaken since the late 50s.

1. *In 1957, as a matter of policy, the Forest Service, U.S. Department of Agriculture (USDA), prohibited the spraying of DDT in specified protective strips around aquatic areas on lands under its jurisdiction.*

2. *In 1958, after having applied approximately 9-1/2 million pounds of the chemical in its Federal-State control programs since 1945, USDA began to phase out its use of DDT. They reduced spraying of DDT from 4.9 million acres in 1957 to just over 100,000 acres in 1967 and used persistent pesticides thereafter only in the absence of effective alternatives. The major uses of DDT by the Forest Service have been against the gypsy moth and the spruce budworm. The development of alternative pesticides such as*

Zectran, which was in operation in 1966, contributed to further reduction in DDT use by the Department.

3. *In 1964, the Secretary of the Interior issued a directive stating that the use of chlorinated hydrocarbons on Interior lands should be avoided unless no other substitutes were available. This regulatory measure, as well as others which followed, was reaffirmed and extended in June 1970, when the Secretary issued an order banning use of 16 types of pesticides, including DDT, on any lands or in any programs managed by the Department's bureaus and agencies.*

4. *Between November 1967 and April 1969, USDA canceled DDT registrations for use against house flies and roaches, on foliage of more than 17 crops, in milk rooms, and on cabbage and lettuce.*

5. *In August 1969, DDT usage was sharply reduced in certain areas of USDA's cooperative Federal-State pest control programs following a review of these programs in relation to environmental contamination.*

6. *In November 1969, USDA initiated action to cancel all DDT registrations for use against pests of shade trees, aquatic areas, the house and garden and tobacco. USDA further announced its intention to discontinue all uses nonessential to human health and for which there were safe and effective substitutes.*

7. *In August 1970, in another major action, USDA canceled Federal registrations of DDT products used as follows: (1) on 50 food crops, beef cattle, goats, sheep, swine, seasoned lumber, finished wood products and buildings; (2) around commercial, institutional, and industrial establishments including all nonfood areas in food processing plants and restaurants, and (3) on flowers and ornamental turf areas.*

EPA highlights the fact that DDT was largely banned in 1972 because it was lipid soluble and bioaccumulated in animals and humans—the same reasons PCBs were banned just 5 years later.

DDT and PCB are very similar compounds. Because of their similar lipid solubilities, both chemicals are bioaccumulative and persist in the body for long periods of time. In fact, DDT and PCBs are still detected in blood samples today, even though both were banned approximately 50 and 40 years ago, respectively.[93]

In this section, I have reconstructed the historical state of the science of DDT research. My historical reconstruction begins in 1945, after Monsanto began producing DDT, and continues through about the next 5 years—to 1950—at which point an overwhelming cache of studies were published and available. It should be noted that after 1950, hundreds of DDT studies were published, but they only refined what scientists already knew about the chemical's bioaccumulation and biomagnification properties.

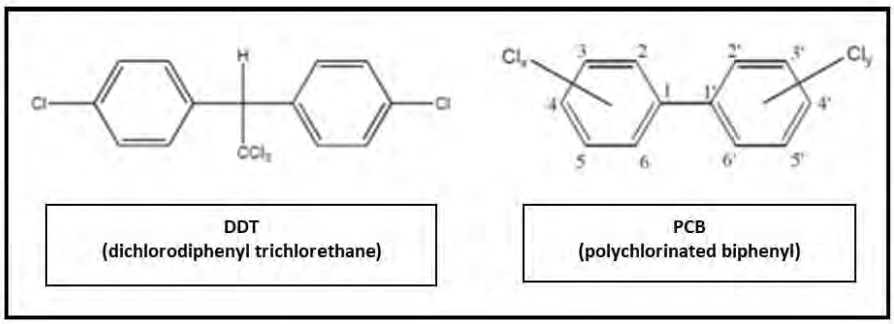
My initial query of published studies in the National Library of Medicine (PubMed) revealed an extensive database of peer-reviewed published works on DDT during 1945–1950. In just this 5-year period, 700–800 studies were published on numerous aspects of DDT. This is an extraordinary number of studies published over such a short period of time. This large collection studies indicates that: 1) the Department of Defense had not conducted many toxicity studies on DDT before 1945 and 2) the initial findings on the potential for bioaccumulation and toxicity in 1945 launched several new studies in many different directions. After vetting the larger database of DDT publications, I identified those that provided the clearest empirical evidence of contemporary knowledge.

Given the similar chemical characteristics of DDT and PCBs, and the knowledge held by the scientific industry during 1945-1950, Monsanto must have known during that period that PCBs would bioaccumulate and biomagnify in people and animals if released into the environment.

8.1. PCBs and DDT Share a Similar Chemical Structure.

As an insecticide, DDT was produced in a technical grade mixture comprising up to 14 similar chemical compounds, of which only 65–80% was the active ingredient, p,p'-DDT. As shown in Exhibit 35, DDT is a relatively simple organic chemical compound: two phenyl groups are attached to trichloroethane. The chemical structure of DDT is similar—but not identical—to that of PCB in that both contain phenyl rings.[67], [94]

Exhibit 35. Chemical Structures of DDT and PCB



Source: ATSDR 2000, 2002.[67], [94]

Both DDT (technical grade) and PCBs (as Aroclors) were complex mixtures of many closely related individual chemical compounds. Theoretically, it is possible to synthesize 45 dichlorodiphenyl trichloroethanes by virtue of different chlorine substitutions made on the two phenyl rings.[95] Likewise, 209 possible different individual PCB congeners can be synthesized, depending on the number and location of chlorine molecules on the biphenyl rings. Different Aroclor formulations were produced for different industrial uses; while each Aroclor mixture differs slightly, they all share physicochemical properties of being highly lipophilic, very stable, and virtually resistant to environmental degradation. Accordingly, these properties are the primary focus of this section of my report because they govern bioaccumulation, biomagnification, and environmental persistence.

Both DDT and PCBs are highly lipophilic. Exhibit 36 shows that DDT and Aroclors 1242, 1254, and 1260 have very similar partition coefficients; thus, they are all similarly absorbed into biological systems.

Exhibit 36. Octanol-Water Partition Coefficients: Comparing DDT and Aroclor

Octanol-water partition coefficient	DDT	Aroclor 1242	Aroclor 1254	Aroclor 1260
Log Kow	6.9	5.6	6.5	6.8

Source: Sources: ATSDR 2002, 2014.[65], [96]

Monsanto, as a manufacturer of both DDT and PCBs, must have known about this similar characteristic of PCBs and DDT early on. Chiefly, because both compounds share the same physicochemical property of lipid solubility and dissolve in the same solvents.

In 1943, (a year before Monsanto started producing DDT), Haller and Busbey described the solubility of DDT as:[97]

> *practically insoluble in water, but is soluble in a wide variety of organic solvents, such as acetone, benzene, xylene, chloroform, carbon tetrachloride, vegetable oils, petroleum oils, and many others. Crude or unrefined kerosene can be used to prepare solutions containing 5 percent of DDT, but refined kerosenes require the addition of 10 to 20 percent of an auxiliary solvent. For this purpose, xylene, cyclohexanone, and alkylated naphthalenes have been used.*

Monsanto sales brochures explained that PCBs were soluble in the very same organic solvents (MONS092683).[57] This common characteristic would have signaled a similar likelihood of bioaccumulation.

8.2. State of the Science, 1945–1950

Insecticidal preparations containing DDT were first brought to the attention of the U.S. Department of Agriculture in October 1942 by the Geigy Co., Inc., New York, NY.[95] From the start, DDT proved to be a very effective insecticide. Once the effectiveness was proved, and DDT started to enjoy wide use in the United States, demand increased, and production soon exploded. Soon afterward, other chemical companies started their own DDT production. One of these companies was Monsanto, which produced DDT from 1944–1957.[11] According to Monsanto's corporate representative, Monsanto was aware of the DDT literature during this time period.[12]

For insecticidal use, DDT was produced in a technical grade mixture comprising up to 14 similar chemical compounds, of which only 65–80% was the active ingredient, p,p'-DDT. As shown in **Error! Reference source not found.**, DDT is relatively simple organic chemical compound: two phenyl groups are attached to trichloroethane.

Early warnings about DDT use started in 1945–1946. DDT's effectiveness in controlling disease transmitted by insects was widely hailed from the very start, but many scientists, public health officials and environmental agencies urged that only low volumes be used to prevent widespread environmental releases. This was because many early studies showed that DDT could kill both terrestrial animals and fish.[98], [99] Moreover, warnings were issued in 1946 (2 years after Monsanto started DDT production) that humans should not come into contact with the oil-DDT formulation because it was lipid soluble and would be readily absorbed through the skin. In a 1946 editorial in the *American Journal of Public Health,*[100] the American Public Health Association (APHA) stated that DDT is "definitely toxic to man and domestic animals" and that it should not be allowed to get into foods or "applied to the skin in an oil solution." Furthermore, the editorial noted:

[11] https://monsanto.com/company/media/q/what-is-monsantos-opinion-on-agent-orange-and-ddt/
[12] Kaley Deposition, Colella v. Monsanto, 11/17/2011, pages 41-43.

> *Therefore, it is important that the suggestions of the Insecticide Division of the Department of Agriculture with regard to standardization and labelling be enforced; and that DDT sprays be not used on cabbage or similar vegetables after the heads have formed, or on crops to be fed to stock, until more is known of their limits of tolerance.*

This caution was warranted because so little was known about DDT. Indeed, even the early studies investigating how DDT actually killed insects were not successful in revealing the mechanism of action. What was known, however, was that DDT must penetrate the insect skeleton and be absorbed into the fat-containing nervous system in order for DDT to kill insects; this penetration was due to the lipid solubility property of DDT.

Kirkwood and Phillips (1946)[101] studied the insecticidal properties of DDT and noted that the earlier insecticidal mechanism proposed by Lauger (1944)[101] was due to the "lipoid" property, stating:

> *Lauger's suggestion is an extension of the Meyer-Overton theory of the mechanism of transportation and "storage" of the general anesthetics. He presented evidence to show that DDT acts on the insect's nervous system…This evidence points rather definitely to a relationship between lipoid affinity and insecticidal activity and as such offers an explanation for the mechanism of action of 1, i-bis(pchlorophenyl) 2,2, 2-trichloroethane and related insecticides as suggested by Lauger.*

In other words, DDT's effectiveness as an insecticide was due to its lipid solubility -- not to a newly developed chemical/biological mechanism.

Two of the earliest studies to evaluate the lipid-solubility property of DDT that governed its bioabsorption and toxicity were published in 1944 (when Monsanto started production) by Smith and Stohlman[102] and by Nelson et al.[103] These studies were published the year Monsanto commenced DDT production.

Smith and Stohlman noted that DDT was absorbed through the skin and that it had a "cumulative action," indicating that its lipid solubility would cause it to accumulate until toxic concentration levels were reached:[102]

> *The toxicity of this compound, its cumulative action, and its absorbability through the skin under a variety of conditions of external application have made it desirable to devise a method for its identification in the tissues and body fluids.*

DDT was not absorbed from the gastrointestinal tract in a water suspension but was absorbed when in a DDT-oil solution:

> *Gastro-intestinal absorption when given in aqueous suspension is irregular and poor, consequently the toxicity of the substance when given in this manner is much lower than when given in olive oil.*

DDT's toxicity was only seen with cumulative exposure as it built up in the body to toxic concentrations, which took 18–80 days:

> *The effects of DDT in experimental animals are cumulative, and small single doses given repeatedly lead to chronic poisoning. In a group of 10 rats of about 80 gm. weight, DDT fed at a level of 0.1 percent in a semisynthetic adequate diet containing 18 percent protein as casein was uniformly fatal in from 18 to 80 days…In rabbits the daily oral administration of 50 mg. per kg. in olive oil, a dose which by itself produces only slight or no demonstrable effects, resulted in cumulative effects terminating in death in from 15 to 23 days after a total dose of from 0.75 to 1.25 gm. per kg. had been given.*

Smith and Stohlman concluded that DDT should be regarded as a health hazard because of its lipid solubility and cumulative toxicity:

> *The toxicity of DDT combined with its cumulative action and absorbability from the skin places a definite health hazard upon its use.*

Nelson et al. also stated that the lipid solubility of the oil-DDT solution controls toxicity and that powdered DDT applied to skin does not cause systemic toxic effects:[103]

> *Lesions caused by DDT in this group were relatively slight, probably because of poor absorption of dry DDT as compared with that dissolved in corn oil.*

In the next year, study designs shifted from using laboratory animals to more environmentally relevant exposures in livestock. Based on the lipid solubility, investigators were interested in quantifying the magnitude of bioaccumulation and biomagnification as DDT was transferred through food chains.

In 1945, Dr. Woodard and his colleagues at the Division of Pharmacology at the U.S. Food and Drug Administration (FDA) published the seminal work on DDT bioaccumulation in breast milk.[89] They theorized that the lipid solubility of DDT enables it to be absorbed into the female body, where it bioaccumulates in the fat-rich breast tissue during pregnancy and that stored DDT is secreted into breastmilk. The DDT in breastmilk would then be absorbed by the suckling offspring to bioaccumulate in the bodies of offspring. This study showed not only that DDT could be transported through livestock and food chains to ultimately target human newborns, but that absorption by livestock could be very significant.[13]

Woodard et al. showed that when dogs were administered DDT for periods of time ranging from 138 days to 2 years, the pups readily bioaccumulated DDT in significant amounts; the DDT was stored in the dogs' fat tissues. Furthermore, DDT was eliminated only slowly from those stores after exposure was discontinued.

Perhaps more alarming—because of the obvious potential for exposures to human newborn children—was the degree to which DDT was secreted into the breastmilk of a lactating female dog. This finding obviously had real-life implications for environmental biological systems, as well as for humans. DDT was soon found to contaminate not only the environment but the U.S.

[13] This study was published around the same time that Monsanto started DDT production. Furthermore, it was published in *Science*, one of the most prestigious and widely read scientific journals. *Science* is the official journal of the American Association for the Advancement of Science [AAAS].

food supply, where women of childbearing age could bioaccumulate DDT and expose their offspring. This first study in dogs seemed to cause considerable concern for public health professionals; as in dogs, human breast milk has a high fat content and could likewise bioaccumulate DDT.

What prompted this study is noteworthy and pertinent to this case. Woodard cited one property as governing bioaccumulation of organic compounds: lipid solubility. He predicted that, based on the single property of lipid solubility, DDT would be bioaccumulative because "The high lipoid-water distribution ratio of DDT suggested that it might be preferentially stored in the adipose [fat] tissues of mammals fed DDT." In other words, he made the logical prediction that DDT bioaccumulates based on its lipid solubility and that DDT is stored in fat.[14]

ACCUMULATION OF DDT IN THE BODY FAT AND ITS APPEARANCE IN THE MILK OF DOGS

> *The high lipoid-water distribution ratio of DDT suggested that it might be preferentially stored in the adipose tissues of mammals fed DDT. The toxicological behavior of this compound pointed also to the possible deposition in body fat.*

Because the dogs were fed DDT, it meant that it was well absorbed from the gastrointestinal tract, distributed in blood, and stored in fat tissue. Exhibit 37 shows that extremely high levels of DDT were detected in fat, with the DDT fat concentration in one dog reaching 4,940 ppm when dosed at 80 mg/kg-day. This means the DDT not only bioaccumulated but also biomagnified. Even after the DDT exposure was terminated for approximately 3 months (80 days), 1 of the 2 dogs still had fat levels of 13 ppm. Both dogs secreted DDT metabolites after dosing was discontinued.

[14] Given PCBs' known lipid solubility, the same prediction could have made that very same year regarding PCBs.

Exhibit 37. Excerpt from Woodard et al.: Bioaccumulation of DDT by Dogs

TABLE 1

ACCUMULATION OF DDT IN THE BODY FAT OF DOGS

Dog no.	Sex	Weight kg	Daily dose mg/kg	Form of administration	Days duration	DDT in fat mg/gm
M–166	f	8.9	10	soln.	747	0.080*
81–196	m	10.0	10	soln.	747	0.024
1–20	f	6.5	50	soln.	443	1.65
81–195	m	10.4	50	soln.	747	4.94
1–35	f	6.9	80	solid	443	0.39
M–171	m	10.3	80	solid	443	0.67
		After discontinuing dose for 81 days				
1–59	f	7.3	80	soln.	138	0.013
1–61	m	9.3	80	soln.	138	0.00

* For purposes of comparison, the intravenous lethal dose of DDT is of the order of 0.04 milligrams per gram body weight.

Source: Woodard et al. 1945.[89]

A further analysis of different fat stores revealed that DDT was distributed uniformly throughout the body, as it was detected in both subcutaneous (skin) and intraperitoneal (abdominal) fat.

Woodard confirmed his assumption that the lipophilic property of DDT is the sole determinant governing bioaccumulation and toxicity because no animals died when dogs were fed dry solid DDT (0/4 dogs), whereas the oil-DDT formulation resulted in the deaths of 14 out of 16 dogs.

In their investigation of the toxicokinetics of DDT, Woodard et al. found that a lactating dog dosed with 80 mg/kg-day-DDT secreted DDT into breast milk at concentrations of 40–60 ppm. In another lactating dog, a single dose of 50 mg/kg-day produced a milk concentration of 50 ppm in just 24 hours, demonstrating that not only was DDT readily absorbed, distributed, and secreted into the milk of lactating animals, but that the transfer was very rapid. Obviously, this shows that the DDT that had rapidly accumulated in the bitch was transferred to her litter of pups and that the same could be expected in humans.

A similar study published in 1945 by Telford and Guthrie also showed that DDT was quickly absorbed and “transmitted through the milk of white rats and goats” to their suckling

young.[104]. This study was important because it was an "environmental" study on livestock that represented the fate and transfer of DDT in the food chain.

In the Telford and Guthrie study, DDT-induced tremors were used as the proxy metric for absorption (instead of direct DDT fat and milk analysis); exhibitions of excitation of the central or peripheral nervous system by the animals would indicate high absorption. Female rats with a 1-day-old litter were fed DDT and developed tremors between 6 and 13 days; their nursing young developed tremors between 14 and 15 days. Telford and Guthrie concluded that DDT was rapidly absorbed in the dams and transferred into the milk, stating, "Evidence was thus obtained that the toxic principle was transmitted through the mothers' milk, since the young showed toxic symptoms before weaning."

In addition, Telford and Guthrie revealed that DDT bioaccumulates and continues to bioaccumulate with chronic dosing, and that it can be transferred between species. When the researchers fed DDT to goats and then fed the goat milk to rats, the rats developed tremors and died within 2–9 days; milk from goats fed DDT for longer periods was more toxic. Telford and Guthrie stated:

> *Milk obtained from goats having received these dosages from 21 to 26 days was much more toxic than milk obtained from animals subjected to shorter periods of treatment. This indicated that DDT continued to bioaccumulate with continued exposures and once in fat tissue it remained for significant periods of time and was not rapidly eliminated.*

Telford and Guthrie also showed that the DDT can be continuously transported through the food chain, and their findings showed biomagnification. For example, milk from a goat dosed with DDT for only 25 days was given to a "half-grown kitten," the kitten died within 3 days, indicating that the DDT level in the breast milk was very high. When goats were administered feed contaminated with DDT and the collected goat milk was fed that to parturient rats (about to give birth), the suckling rat pups exhibited DDT toxicity.

Like Woodard et al. (1945),[89] Telford and Guthrie also concluded that the lipid-solubility of DDT controls bioabsorption and produces the toxic effects they observed, stating:[104]

> *There is evidence that the toxic principle is concentrated in the fat globules of the milk, for butter, prepared from the milk of goats under similar treatment, when fed to rats produced typical tremors in the latter within 24 hours.*

Telford and Guthrie noted that their findings had real-life implications for the transfer of DDT through the environment and, ultimately, for exposure to humans:

> *The data strongly suggest the need for more intensive research on the toxicity of milk from dairy cows ingesting DDT residues either from sprayed or dusted forage plants or from licking themselves after being sprayed or dusted with this insecticide.*

These studies compelled other scientists to focus on environmental exposures and to determine whether the U.S. food supply was now at risk. As indiscriminant use of DDT was expanding, with large regional areas contaminated by widespread airborne spraying of DDT, pollution was now being taken seriously. The focus of scientific investigations turned to measuring the concentrations of food residues and making a determination regarding whether DDT residues in different commodities in the U.S. food supply could pose risks to the general population.

In a second June 1946 editorial in the *American Journal of Public Health*, the APHA took a position on protecting human health from exposure to, and toxicity from, DDT.[90] This was essentially a cautionary statement noting that, while DDT was a "wonder insect killer," exposures to humans was a real concern and must be taken into account. APHA believed it was its professional responsibility to issue a caution that DDT is highly lipophilic and will bioaccumulate and biomagnify if used to spray crops or directly applied to human skin in an oil-DDT formulation because no regulations existed in 1946 regarding the judicious and safe use of DDT. The other emerging concern was that DDT was persistent.

The editorial was written by Dr. Bishopp. The APHA specifically reached out to Dr. Bishopp (who was at the U.S. Department of Agriculture; the agency that had primacy over how DDT could be used) to prepare a Special Review Article. To summarize, Bishopp issued a forewarning that DDT posed real threats to public health because it was being released in massive levels to the environment. This could have catastrophic consequences. He noted that while DDT is a very powerful weapon against disease-carrying insects, scientists needed to begin looking more carefully at the potential human health impacts.

Bishopp also issued a prescient forewarning in 1947 about the longevity of environmental contamination from widespread use of DDT. This warning would prove to be correct. Although Bishopp could not know at the time, the one physical characteristic of DDT he noted was its "persistence," which would later cause DDT to be identified as a global pollution problem (as would PCBs). Bishopp noted that, while persistence was an excellent property for DDT as an insecticide, great care should be exercised to prevent contamination of the U.S. food supply—with specific reference to protecting livestock. He stated:

> *One of the outstanding characteristics of DDT is its persistence. In fact, this is perhaps the major element in making it superior to many other insecticides. This persistence, however, makes it necessary to use care when applying it on crops or products intended for food or feed…The Bureau of Entomology and Quarantine does not recommend DDT for use on cabbage or similar vegetables after the heads or other edible parts are formed. Likewise, that bureau does not recommend its use on alfalfa, corn, or other crops to be fed to stock, especially dairy animals, until more is learned of the fate of small amounts ingested, especially with fatty materials.*

By 1947, even major chemical companies were actively participating in, and funding research on, the topics of bioaccumulation, biomagnification, and human health risks from DDT. For example, American Cyanamid Company provided funding for a study by Howell et. al (1947) to investigate DDT bioaccumulation into cows and subsequent milk contamination. [105] This study was launched under actual environmental exposure conditions to determine whether the DDT sprayed on cows (to kill flies) was absorbed by the cows and secreted into milk that could

potentially reach U.S. consumers. Spraying cows and dairy barns with DDT was becoming a concerning practice by 1947 as a method to control flies in dairy barns, as Howell noted:

> *considerable interest was created in the possibility that cows sprayed with this insecticide for fly control might produce milk containing toxic amounts of DDT.*

Alarmed by earlier findings that lipid-soluble DDT was readily absorbed through the skin of other livestock and laboratory animals, Howell et al. initiated a series of investigations to determine whether DDT sprayed on the hides of cows absorbs and bioaccumulates. The researchers stated their concern:

> *When it was shown that DDT may be absorbed through the skin of animals and that animals fed massive doses of this material produced milk containing toxic doses of DDT, considerable interest was created in the possibility that cows sprayed with this insecticide for fly control might produce milk containing toxic amounts of DDT. To test this hypothesis a cooperative experiment was planned to show the effects of very heavy spraying and also the effects of the spraying schedule suggested for hornfly control in this area.*

The results reported by Howell et al. show detections of DDT in milk from all cows after the 3-week exposure period during which cows were either sprayed daily or every 14 days with varying DDT concentrations ranging from 0.25–5.0% DDT, which corresponded to the actual exposure conditions that farmers were using. These exposures resulted in all cows secreting DDT in milk, with a maximum concentration of 33.6 ppm in milk from a cow sprayed for 20 days. [105]

Their findings also showed that once cows were sprayed and bioaccumulated DDT into their fattissue, the DDT remained and was not quickly eliminated. DDT was still detected in the milk for at least another 3.5 months (120 days). Daily measurements showed that DDT-contaminated milk was still detected on December 1, although DDT exposure had been terminated on September 30. [105]

In addition to the concerns regarding bioaccumulation of lipophilic DDT in milk (which was confirmed in 1946), scientists were concerned about the U.S. meat supply and predicted that beef muscle fat could also be contaminated. A study by Carter et al. (1948)[106] showed that DDT remained resistant to degradation, no matter the method of cooking, once DDT was absorbed into muscle fat tissue: "The results of the chemical analyses, given in Table 1, indicate that the DDT in the beef was not materially decomposed or lost during the cooking." When beef cattle were fed DDT-contaminated hay, the highly lipophilic compound accumulated in muscle fat and was not appreciably degraded, even after four different cooking methods.[106]

In 1947, Rubin et al. investigated the bioaccumulation of DDT in eggs laid by chickens administered feed with different DDT residue concentrations.[107] The DDT bioaccumulation appeared to follow a dose-bioaccumulation relationship.

Rubin et al. concluded:

> *It is apparent that deposition of DDT in the eggs increased as the dietary intake of this compound increased but reached a maximum when the intake was 0.125% of the diet.*

One year later, in 1948, biomagnification through the food web became a major concern for public health officials and regulatory agencies, who now saw that low levels of DDT in the U.S. food supply were producing very high levels in fat stores. This prompted Dr. Fitzhugh, of the Food and Drug Administration, to conduct a biomagnification study:[20]

> *Because small amounts of DDT in animal food cause the storage of large amounts in animal products which are used in enormous quantities by man, the question of the safety of DDT on and in food products becomes critically important…The general availability and effectiveness of DDT as an insecticide introduce the possibility of its widespread occurrence in food products. The most serious source of danger from the use of DDT is the repeated ingestion of small amounts that cling to forage, fruits, and vegetables that have been treated with this insecticide.*

The Fitzhugh (1948) study was intended to evaluate the possibility that widespread use and availability of DDT resulting in low levels of DDT detected in fat-containing foods during FDA's food surveillance could inexorably build up as DDT was transferred from one animal to another up the food chain. The greatest impact of biomagnification would be in humans.

In effect, he was raising the same issue as Bishopp (1946).[90] While Bishopp was only able to predict biomagnification through the complex food web, Fitzhugh and his staff at the FDA were in a position to *test* this possibility. As discussed previously, many at the time were of the opinion that DDT was still safe to use because it was virtually nontoxic, based on a single acute dose. Now knowing that cumulative exposures to livestock led to bioaccumulation and secretion into milk because DDT was so highly lipophilic, each subsequent exposure led to more DDT accumulating in the fat tissue increasing the body burden. In short, DDT levels were compounded and magnified with continuous daily exposures where the concentration in body fat far exceeded the concentration in their feed .[20]

> *The storage of DDT in the tissues, especially in the fatty tissues of animals ingesting small amounts, has been demonstrated in cows, monkeys, dogs, rats, rabbits, and poultry. DDT has been shown to be secreted in the milk of cows, goats, dogs, and rats. Other animals fed the milk from the DDT-treated animals showed toxic symptoms. All the DDT in the milk appears to be concentrated in the butterfat portion and to be transferred to the butter; therefore, a relatively small amount of DDT in the whole milk results in a significant amount in the butter. The quantities of DDT that are stored apparently depend both on the level of ingestion and on the length of time over which the intake occurs.*

Fitzhugh's major concern regarding the food supply was that each incremental chronic ingestion of contaminated food (even if the dose was low) could ultimately result in the high levels of DDT in fat stores. In other words, he was stating the obvious: chronic doses are additive, amplifying the toxic effect, with the sum of each dose eventually equaling a very large single dose.

It should also be noted that human infants were then being identified as the most sensitive subpopulation:

> *In long term experiments dosage levels of DDT from 10 to 200 p.p.m. in the diet produce relatively similar amounts of DDT in the fat (Table I). An animal may store amounts equivalent to several acute intravenous lethal doses without showing any obvious signs of intoxication. The accumulation of appreciable quantities of DDT in animal tissues at low dietary levels (all levels appear to produce storage in fat) poses a difficult problem, since many animal products are, used for human consumption. This may be especially important in the case of infants, whose chief food is milk. The presence of small amounts of DDT in animal food, therefore, assumes the same importance as relatively larger amounts on fruits and vegetables consumed directly by man.*

Fitzhugh's empirical evidence of this biomagnification phenomena demonstrated that a low daily dose was biomagnified in the tissue of rats. Some of the rats had a biomagnification factor of up to 27-fold. That is, the concentration in body fat (perirenal; kidney fat) was 27 times the dose concentration the rat was fed (although there was much variation among the rats).[20]

Fitzhugh noted that, when small daily doses yielded the biomagnified DDT fat levels, insidious and unexpected toxic effects expected from a single large dose were produced. He reasoned that DDT is sequestered in fat tissue when administered at lower levels, where it is safely stored and cannot produce DDT-induced neurotoxicity. This is because toxic chemicals are unable to produce toxic effects when they are bound to proteins or fats. It is only when they become "unbound" and circulate in a "free" state that they become mobile in the blood circulation and can reach the brain or peripheral nerve to attack the nervous system. There is a dynamic equilibrium between DDT stored in lipoproteins in the blood and in fat tissue. Fitzhugh knew that when the ratio between bound and free DDT shifts with fat loss (as occurs with illness, disease, or dieting), more free DDT becomes available to reach the target organ (nervous system). Fitzhugh tested this phenomenon by removing the rat food (essentially mobilizing more free DDT because fat was now being consumed as an energy source) and confirmed that DDT-

induced tremors were produced. This showed the additional risks DDT poses to the U.S. general population as individuals intentionally or unintentionally (disease and illness) mobilize or lose body fat, since DDT is then free to attack the liver or central nervous system. It would also increase the cancer risk: [15] [20]

> *The withdrawal of food from animals on high dosage levels of DDT produces characteristic DDT tremors. This effect occurs both in starvation experiments with DDT-treated animals and in DDT-treated animals made sick by an infection {2). In the latter case the animals supposedly were metabolizing their body fat containing the DDT in the same manner as a starved animal. This effect could be important in cases of human illness where there is an appreciable storage of DDT in the body.*

The 1948 Fitzhugh study presented clear, simple, and unequivocal empirical evidence that DDT bioaccumulate and biomagnifies, and that this property is directly and unmistakably due to DDT's high lipid solubility. Furthermore, Fitzhugh did not require any elaborate laboratory equipment or sophisticated study designs to prove these facts. He predicted DDT would bioaccumulate and biomagnify and used simply designed experimental methods to prove his prediction. Fitzhugh employed the same experimental animals, study designs, and methods that were used in the late 1930s.[16]

A more sophisticated study of absorption, distribution, and elimination of DDT and dichlorodiphenyldichloroethane (DDD), which have the same lipophilic properties, was published in 1949 by Finnegan et al.[108] Like the Howell et al. (1947) study,[105] this too was funded by a chemical company–Rohm and Hass Company. By 1949, DDT had been in widespread use, with massive quantities released into the environment. Finnegan's study investigated the toxicokinetics and combined absorption, storage, and excretion of DDT. After dosing dogs with DDT and DDD (a major degradation product of DDT) for 2 and 4 weeks,

[15] Fitzhugh and Nelson had shown just a year earlier that DDT causes cancer[123]
[16] Monsanto could have performed a study identical to Fitzhugh's investigation in the late 1930s on PCBs.

Finnegan et al. measured the content of these two pesticides in all major organs. Their results are tabulated in Exhibit 38. Not surprisingly, fat tissue and organs rich in fat had the highest concentrations of both compounds.

Exhibit 38. Excerpt from Finnegan et al.: DDD and DDT Content in Dog Tissues After Oral Administration

TABLE I.
DDD and DDT Content of Tissues of Dogs to Which the Insecticides Had Been Administered Orally Daily for Periods of 2 and 4 Weeks.

	Insecticide content, mg per kg of tissue									
Insecticide	DDD					DDT				
Duration	2 wks		4 wks			2 wks		4 wks		
Dog No.	D-4	D-5	D-1	D-2	D-3	T-4	T-5	T-1	T-2	T-3
Liver	0	0	1.6	0	24	0	0	0	0	0
Kidney	15	4.3	13	14	15	4.9	0	14	7.2	9.6
Heart	3.8	0	11	12	13	0	3.4	4.9	8.1	3.4
Brain	0	0	3.5	4.1	5.2	1.3	0	2.5	3.9	1.2
Lung	0	0	1.9	3.9	lost	0	0	0	0	0.8
Pancreas	0	0	8.9	29	12	0	3.4	14	9.4	8.8
Spleen	0	1.7	0	12	4.7	0	0	2.2	3.6	0
Adrenal	0	0	150	0	210	0	0	83	63	62
Fat	76	270	880	360	300	29	100	910	400	200
Muscle (gastroc.)	7.6	5.2	lost	20	28	8.4	5.5	12	14	18
Skin	90	7.2	28	128	18	82	73	0	6.4	3.3
Mammary gland	—	—	—	—	—	—	—	2.2	—	21
Fecal excretion mg/kg body wt, 48 hr	0.9	4.2	3.9	2.2	3.9	lost	0.03	0.01	0.5	0.8

Source: Finnegan JK, Haag HB, Larson PS. 1949.[108]

In a set of additional experiments, Finnegan et al. investigated whether DDT could pass the placenta circulation from the maternal blood supply to the developing fetus. In these experiments, some of females became pregnant during the dosing exposure and bore litters of pups, some of which were stillborn. The surviving pups were killed before they were able to suckle breast milk. The researchers repeated the earlier experiments and measured the body burden levels in both the newborn (but not sucking pups) and stillborn pups. With this experimental protocol preventing the pups from suckling breast milk, they could directly determine if DDT crossed the placental barrier to expose the developing fetal pup. Again, this experiment was based on the prediction that lipid-soluble DDT would readily pass the placental barrier, as other important lipids and lipoproteins do. What Finnegan et al. found was an unexpectedly high bioaccumulation of DDT in the pups (although they noted that they lost part

of the sample for the T-1 pups, which accounts for the relatively low DDT levels detected in those dogs). They stated:

> *Analysis of the pooled carcasses of the 5 stillborn pups from one of the 4-week DDD dogs (D-1) showed a content of 3.7 mg per kg DDD. Similar analyses of individual carcasses of (the 2 newborn pups from dog T-1 and the 2 newborn pups from dog T-3 (both 4-week DDT dogs) gave average values of 1.3 mg per kg for the first pair and 0.04 mg per the for the second. It was thought that the latter result was low owing to possible loss of part of the sample. These results demonstrate transfer of both DDD and DDT across the placenta.*

Their findings added to concerns regarding DDT for two reasons. First, they showed that human lifetime exposures do not start after birth with breastfeeding, but that exposures and bioaccumulation start in the womb. Second, their results raised the possibility of birth defects and developmental abnormalities since DDT exposures to the fetus start very early in development—before organogenesis—when maternal–fetal blood connection is first established. The scientific work to this point had shown biomagnification during breastfeeding of the newborn, but fetal abnormalities were a now a concern because the fetus had been shown to be exposed to the lipid-soluble DDT. In fact, Fitzhugh concluded that transplacental transfer of DDT was greater than newborn suckling of breastmilk:

> *This again is indicative of a high degree of placental transfer of DDT and further suggests that the fetus is more liable to the accumulation of DDT than is the suckling offspring, despite the fact that DDT has been shown to be secreted in the milk*[17].

Once again, Finnegan et al. identified DDT's lipid solubility as the governing property of DDT. Moreover, they noted the same scientific processes that I previously discussed with regard to the

[17] Given that DDT and PCBs share the same lipid solubility property, Fitzhugh's conclusion could have been extended to PCBs. Based on Fitzhugh's study, PCBs should have been understood to be absorbed from maternal blood into fetal blood, resulting in exposure of the developing fetus in the womb, with unknown health effects.

Meyer-Overton rule explaining bioaccumulation of both DDT and DDD. That is, both compounds are chemically similar, and both are similarly soluble in olive oil.

> *It seems that, in general DDD and DDT were deposited in fat to a similar degree. This is in agreement with the thesis of von Oettingen and Sharpless that since the 2 compounds have similar solubility's in olive oil they would probably be stored to about the same degree in fat.*

It should be noted that, although this was the first empirical evidence of a specific lipophilic compound transferred from maternal blood to fetal blood (namely DDT and DDD), it was well-established a decade earlier—in 1937—that lipids and lipophilic substances readily pass through the placental circulation and are absorbed into the developing fetus.[109], [110] Finnegan et al. noted that this new finding was more significant than those of earlier studies revealing that DDT was secreted into breast milk. Direct blood transfer of lipid-soluble DDT from mother to fetus increased body burden more than subsequent newborn suckling of breastmilk:[108]

> *This again seems indicative of a high degree of placental transfer of DDT and further suggests that the fetus is more liable to the accumulation of DDT than is the suckling offspring, despite the fact that DDT has been shown to be secreted in the milk.*

To summarize, the chemical industry knew by 1949 that lipophilic chemical compounds like DDT readily cross the placental circulation to the fetus and are also secreted into the mother's milk. This means that the body burden of such lipophilic compounds would already be significant at birth and that the body burden would only increase with subsequent breast-feeding.

Additionally, when bioaccumulation of DDT fetal and newborn body burden is considered based on body weight, newborns would have the largest body burden at this stage of life. By 1950, scientists had established that DDT bioaccumulated and biomagnified in the food web and that the developing fetus and newborn were of growing concern. Newborn animals not only accumulated high levels of DDT, but they were at particular risk because they were undergoing

organogenesis. While many previous studies dosed animals at elevated DDT levels (thought to be above what the general population would receive in its daily diet) in experiments, it was unknown whether DDT would bioaccumulate at lower doses—those levels closer to the "assumed" daily dietary intakes. However, no governmental agency had started a food surveillance-sampling program at this time, so the residue levels were unknown. To determine if lower doses would also be bioaccumulative and biomagnify, Laug et al. (1950) conducted experiments at very low doses (far lower than would be reported in food residue studies).[21] The lowest DDT level they used was 1 ppm. They explained their rationale:

> *Storage within the organism of any toxic substance foreign to its tissues may he regarded as a potential hazard. As reported from this laboratory the DDT content of the adipose tissues of animals consuming high concentrations of DDT in their diets can be 100 times as great as in other tissues. While these data clearly indicate DDT storage in fat when DDT is ingested in large amounts, it does not necessarily follow that storage would occur when very small amounts of DDT are ingested. In view of the widespread use of DDT as an insecticide, the content of a variety of foods may be expected to be of the order of 1 .0 p.p.m. more or less.*

Exhibit 39 presents Laug et al. findings that food residues as low as 1 ppm did indeed bioaccumulate and biomagnify in perirenal fat.

Exhibit 39. Excerpt from Laug et al.: DDT Content in Perirenal Fat, by Dietary Level of DDT

TABLE 1

The storage of DDT in the perirenal fat of rats at various dietary levels of DDT

P.P.M. DDT IN DIET	P.P.M. DDT IN PERIRENAL FAT								STORAGE RATIO†	
	After 15 weeks		After 19 weeks		After 23 weeks		After 27 weeks			
	M	F	M	F	M	F	M	F	M	F
Control*			7.8	6.2		7.1	8.1	9.4		
0.12			3.4	4.5						
1	15	20	24	38	21	25	17	33	21	29
	11	16	27	30	33	33		37		
5	61	88	68	108	64	111	47	106	12	20
	45	107	62	106	60	110	54	74		
10	65	137	79	155	84	165	78	132	8	15
50	350	642							6	12
	217	533								

* Additional control animals housed in different rooms: the fat of two year-old males contained 13 and 13 p.p.m., respectively; the fat of two 8-month-old males contained 10 and 5.8 p.p.m., respectively.

† $\frac{\text{Concentration of DDT in Fat}}{\text{Concentration of DDT in Diet}}$. The concentration of DDT in the fat represents the average of the 15, 19, 23 and 27-week groups.

Source: Laug et al. 1949.[21]

As shown, a concentration as low as 1 ppm DDT in the diet was not only bioaccumulated, but the storage ratio (DDT fat concentration/DDT in diet) was much higher at lower doses. This means that the ability of DDT to bioaccumulate was higher at lower doses. Their results also showed a gender sensitivity in that female rats accumulated DDT to much greater fat concentrations, which, in turn, meant they would transfer larger amounts of DDT to their offspring. Females fed a diet with DDT residues at 1 ppm resulted in fat concentrations of 20, 38, 25, and 33 ppm at 15, 19, 23, and 27 weeks, respectively. Another interesting finding from the Laug et al. study is that DDT bioaccumulation occurred even in the control animals (shown in 0 as Control*). This is significant because it revealed that the environment was ubiquitously contaminated with DDT. Despite the fact that control animals were not dosed with DDT and were housed in a separate animal room, DDT was detected in their body fat. Laug et al. concluded this result showed extremely low levels of DDT residues in their purchased commercial rat chow and even at these "extremely" low dietary levels, animals were bioaccumulating DDT. Laug et al. also stressed that this demonstrated the "avidity" of DDT in that even miniscule amounts could lead to bioaccumulation:

> *The finding of DDT in the fat of the control animals demonstrates the avidity with which the adipose tissue can accumulate DDT from extremely small dietary residues. It should be emphasized that the finding of DDT in the fat was not restricted to the animals serving as controls for this series, but was observed also in other animals housed in different laboratories for longer periods of time (see footnote, table 1).*

He further stated that there was no "floor" (minimum dose level) below which DDT would not bioaccumulate.

> *DISCUSSION. The experiments reported here show that very small quantities of DDT in the diet are reflected in storage in the fat of rats. Furthermore, it appears that as the amount of DDT offered the rat in its diet decreases, the percentage thereof which goes into storage increases. It. may be concluded therefore that there is no "floor" of dietary concentration below which the storage of DDT does not occur.*

Laug et al. prepared a graph demonstrating how DDT bioaccumulation inexorably increases with chronic exposure over a 27-week exposure period (Exhibit 40). This graph mirrors the types of exposures that would be expected in the U.S. general population.

Exhibit 40. Laug et al. Excerpt: Increase of DDT Storage in Rat over Time

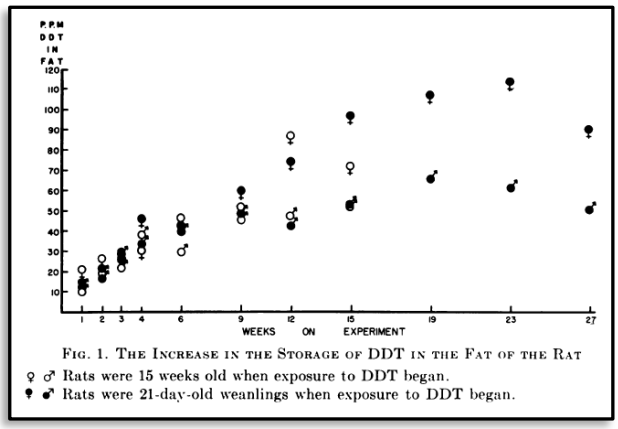


FIG. 1. THE INCREASE IN THE STORAGE OF DDT IN THE FAT OF THE RAT
♀ ♂ Rats were 15 weeks old when exposure to DDT began.
♀ ♂ Rats were 21-day-old weanlings when exposure to DDT began.

Source: Laug et al. 1949.[21]

After showing that DDT body burden levels would build to potentially toxic levels with chronic exposures, Laug et al. turned their attention to the elimination rate to determine how fast DDT would be secreted in stool or urine if DDT exposures were discontinued. DDT would be eliminated very slowly, with fat stores still at high levels (73%) after 1 month at a low dose (1 ppm); at a higher dose (50 ppm), DDT would still be elevated after 3 months (26% in female rats).

Two years before the Laug et al. study was published (1950), Carter (1948) published one of the first analytical surveys of DDT.[111] His results were troubling because he detected DDT at levels much higher than 1 ppm (the level used by Laug et al). Working in collaboration with food cooperatives and industry, he investigated how DDT was routinely used and followed the DDT literally from the "ground up" to measure bioaccumulation and other impacts on food chains in order to get a clear picture of the potential contamination of the U.S. food supply. Their goals were as follows: 1) determine the DDT residues on fruits, vegetables, and forage crops; 2) measure the absorption of DDT residues by plants and its translocation into the edible portions from applications to the aerial parts; 3) measure absorption and storage of DDT in the organs and tissues of farm animals that received small amounts ingested with the food; 4) quantify DDT content of milk from cows fed silage containing DDT residues; 5) evaluate the effect of cooking

meat from animals that had stored appreciable amounts of DDT in their tissues as a result of having been fed rations containing this compound; and 6) measure the DDT content of eggs from hens receiving DDT in their feed. Carter's experiments not only quantified the residue amounts of DDT that would contaminate specific food items, but provided a wider perspective on the complex fate and transport environmental processes controlling how DDT moved and biomagnified through the various trophic levels. For example, Carter determined what amount of DDT deposited in soil would be translocated up into the edible plant parts that would be fed to livestock, where the DDT would bioaccumulate into fat tissue of fish, poultry, meat, milk, eggs, etc. His analysis showed that potential DDT contamination of food was likely well above levels of 1 ppm that were "assumed" by Laug et al. in 1950.[21] For example, cows were raised on pea vines and had a residue concentration of 50 ppm (Exhibit 41).[111]

Exhibit 41. Excerpt from Carter: DDT Residues on Various Crops

TABLE I. DDT RESIDUES ON CROPS

Crop	DDT Treatment[a]	Time of Sampling	DDT Residue, P.P.M.
Apples	Sprays, 1 lb. per 100 gal.	Harvest	1–12.5
Peaches			
Unbrushed	Sprays, 1 lb. per 100 gal.	Harvest	6–23
Brushed	Sprays, 1 lb. per 100 gal.	Harvest	3–14
Pea vines	Aerosols, 0.3–0.5 lb. per acre	Maturity	15–50
	Dusts, 0.5–1 lb. per acre	Maturity	2–10
Shelled peas	Dusts, 0.5–1 lb. per acre	Maturity	None
Alfalfa	Dusts, 1–2 lb. per acre	Hay cutting	2–48

[a] 4 cover sprays for apples, 2 for peaches.

Source: Carter 1948.[111]

Carter attributed the total environmental "load" in all food to be due to the stability or persistence of DDT because, even when DDT was applied early in the growing season, it still contaminated the crops at harvest and would then be bioaccumulated into livestock administered the contaminated feed:

> *Insecticide formulations containing DDT applied to field crops during the growing season generally result in residues which persist until the crop is*

> *harvested. When forage crops containing large amounts of DDT residue are fed to farm animals, DDT may be stored in the tissues and eliminated in the milk.*

After slaughter and analysis of different butchered cuts of meat, pigs fed corn meal and ground beef containing 5 ppm DDT revealed that the lipophilic property of DDT was the sole determinant factor in the disposition of DDT in fat:

> *The pigs were butchered and the carcasses separated into three portions—lean meat, leaf fat, and external plus intramuscular fat. The amounts of DDT from the two lots were 2 and 1.7 p.p.m. in the lean meat, 15.6 and 11.4 p.p.m. in the external and intramuscular fat, and 17.6 and 11.4 p.p.m. in the leaf fat.*

DDT content in milk depended on the silage DDT residue concentration in food, which ranged from zero to 25 ppm. In eggs, the concentration was much higher. When chickens were fed a diet with DDT levels of 0.031, 0.062, 0.125, and 0.250% DDT, the concentrations found in the eggs were 0, 180, 240, 360, and 320 ppm, respectively, showing significant biomagnification even when limiting the food chain from chicken to egg. Based on the totality of his analyses, Carter attributed contamination of the food supply on DDT's environmental persistence and lipid solubility:

> *CONCLUSIONS Insecticide formulations containing DDT applied to field crops during the growing season generally result in residues which persist until the crop is harvested. When forage crops containing large amounts of DDT residue are fed to farm animals, DDT may be stored in the tissues and eliminated in the milk."*

By 1947, the U.S. Department of Agriculture was concerned that indiscriminant use of DDT could lead to contamination of the U.S. milk supply after considering all the published studies summarized here. Shepherd et al. (1949) conducted a controlled environmental study on feeding milking cows both alfalfa and pea vine silage with various residue levels of DDT.[112] They stated the department's alarm:

> *Insecticides containing DDT now are being used on various crops grown as feed for milking cows. The relationship between the amount of DDT residue on the crop when fed, or the amount of DDT ingested by the cows, and the amount of DDT that may appear in the milk is not too well known. It is possible that enough DDT may be secreted in the milk to make it detrimental to consumers, especially if consumption of such milk is continued over a long period of time, since Kunze et al. (3) have reported that as little as 5 p.p.m, of DDT in the diet of the rat for 4 to 6 months will produce histopathological alterations of the liver.*

They identified the seminal previous studies that were begun in 1946 that prompted their work:

> *Carter* et al. *(1) fed pea vine silage to milking cows at the rate of 3 lb. per 100 lb. of body weight. The silage contained 2.7 to 5.4 ɣ, of DDT per g. on a fresh basis and 7.7 to 18.7 7 on a dry weight basis. The daily intake of DDT per cow was approximately 44 to 88 rag. The DDT content of the milk was less than 0.5 y per g. Wilson* et al. *(5) found 15 V of DDT per g. in the milk from cows fed pea vine silage that provided an intake of about 1.5 g. of DDT per day per 1,000 lb. of body weight. These same investigators also found 44 T per g. in the milk from a cow that received 24 g. of DDT per day. This report gives the results of recent studies showing the concentration of DDT in the milk from cows fed alfalfa hay that had been treated with DDT under field conditions.*

Although their study was a field study, Shepherd et al. applied the amount of DDT that was routinely used to control the potato leafhopper:

> *In August, 1947, a field of alfalfa, from which the third cutting was to be taken, was treated with different amounts of DDT by means of an aerosol machine. Part of the field was treated with 0.6 lb. of DDT per acre, the rate usually recommended for control of the potato leafhopper, and harvested 20 days later.*

Data for one cow show that DDT accumulated in milk while the cow was fed contaminated pea vines and after the DDT was terminated (on April 14, 1948).

Their findings were a stark warning that the entire U.S. milk supply could be contaminated with DDT. Shepherd et al. also showed that once DDT bioaccumulated in milk cows, it continued to contaminate the milk for long periods of time after exposure ceased (Exhibit 42).

Exhibit 42. Excerpt from Shepherd et al.: Summary of Findings

SUMMARY

1. Alfalfa treated with 2.4 lb. of DDT per acre, in the form of an aerosol, and fed to cows at the rate of 1 lb. of hay per day per 100 lb. of body weight produced milk containing up to 10.1 γ of DDT per g. or 259.1 γ per g. of butterfat. The daily intake of DDT was as high as 903 mg. and the output in the milk was as high as 265 mg.

2. Alfalfa treated with 0.6 lb. of DDT per acre and fed to cows at the rate of 1.5 lb. of hay per 100 lb. of body weight produced milk containing up to 0.9 γ of DDT per g.

3. The output of DDT in the milk varied from 5 to 30 per cent of the intake. The DDT appeared in the milk after a very few days of feeding, and in one case was present in appreciable quantities after 3 days of feeding.

4. After the feeding of DDT hay was discontinued, DDT was detected in the milk for 160 to 170 days when large quantities of DDT had been fed and for only 30 to 40 days when small quantities had been fed.

Source: Shepherd et al. 1949.[112]

8.3. The link between DDT Food Residues and Body Burden continued to be developed after 1950.

All of the DDT studies described above were published 1944–1950 and demonstrated that DDT's high lipid solubility resulted in bioaccumulation and biomagnification in animals and humans. After studies through 1950 provided overwhelming empirical evidence of DDT bioaccumulating and biomagnifying, scientists and the regulatory community continued to further quantify food contamination, as well as body burden in the U.S. general population. I summarize these efforts in the remainder of this section.

Once it had been established that DDT food residues were elevated, the next step was to confirm that was directly linked to increased body burden in the general U.S. population. Pearce et al. (1952), from the U.S. Public Health Service, began a surveillance study in 1949 to measure DDT and dichlorodiphenyldichloroethylene (DDE) in human fat.[113] They initially measured the levels in individuals who had known high exposures to DDT. In 1952, Pearce extended those initial investigations to measuring the DDT concentration in fat stores from persons who had no known exposure to DDT or who had not been exposed for "some time." This group was assumed to represent the U.S. general population exposed to DDT residues only through consuming food. Pearce et al. based their sampling on two cohorts—neither of which had known direct DDT exposures—and found that both had bioaccumulated very significant levels of both DDT and DDE in their fat stores.

Based on this data, Pearce et al. stated that the levels of DDT "in the fat of individuals of the general population arises mainly through contamination of a number of common foodstuffs." They also raised the possiblity that DDT health risks may have been previously underestimated because those studies had not measured DDE levels, so the toxicity from this second group of DDT-like compounds would have been ignored. Pearce et al. showed that both DDT and DDE were found together in every sample.

> *If DDT is slowly degraded after deposition in the fat, it would seem of great importance in assessing any potential danger from food contamination with DDT. In any case, the evidence for the occurrence of substantial proportions of DDE suggest that the possible health hazards involved in the widespread use of DDT need to be reconsidered and further investigated.*

In a subquent experiment to verify the results of Pearce et al. that members of the general population had significant levels of DDT in their fat and that this was not a spurious finding, Mattson et al. (1953) (also at the Public Health Service) obtained and measured DDT in human archival autopsy fat specimens dating back to 1938 and 1940 (prior to the manufacture of DDT in approximately 1944).[114] They found no evidence of DDT or DDE, which they assumed were breakdown products. A summary of their DDT and DDE data is presented in Exhibit 43.

Exhibit 43. Excerpt from Mattson et al.: DDT and DDE in Human Archival Fat Specimens

Table XI. Analyses of Human Fat Samples Taken in 1938 and 1940

Year Taken	Net Grams of Fat	Wave Length, Mμ: 520 Corrected[a] absorbance	597 Corrected[a] absorbance	Equivalent of[b] Absorbance in Terms of: p,p′-DDE, γ	p,p′-DDT, γ	p,p′-DDE, p.p.m.	p,p′-DDT, p.p.m.
1938	2.5	0.013	0.008	1.1	0.8	0.4	0.3
1940	1.9	0.004	0.008	0.1	0.9	0.1	0.5
1940	1.6	0.010	0.009	0.7	1.0	0.4	0.6

[a] Corrected for reagent and Davidow column blanks.
[b] No Schechter-Haller colors in evidence.

Source: Mattson et al. 1953.[114]

With this verication step completed, Mattson et al. stated, “The writers believe that DDT and DDE are contaminants of human fat of the general population.” Thus, the DDT residue levels quantified by Carter now appeared to be directly linked to the general U.S. population. In a fairly comprehensive analysis of DDT residues in the general food supply, Walker and his colleagues at the Public Health Service (1954) launched a detailed analysis of the U.S. food supply based on actual meals that were being consumed by average Americans (Exhibit 44).[115] They stated:

> *To determine the amounts of DDT and DDE ingested during normal food intake, 18 meals were obtained from restaurants and 7 were obtained from a correctional institution. Most of the food prepared by the restaurants was not locally grown. Much of the food consumed at the correctional institution was produced within the institution itself. Regional items, such as fresh sea food and unusual foods, were avoided, so that a representative cross section of food items consumed by the public could be obtained. Home-cooked meals also were avoided because of the difficulty of obtaining a representative cross section.*

Exhibit 44. Excerpt from Walker et al.: DDT and DDE Content of Typical U.S. Meals

Table I. DDT and DDE Found in Typical Restaurant and Institutional Meals

Meal	Total Weight (Including Beverage), Grams	Total Found, γ DDT[a]	Total Found, γ DDE[b]	Ratio of DDE/DDT
Morning				
1	527	27.5	12.5	0.46
2	443	62.5	30.5	0.49
3	522[c]	59.5	24.5	0.41
4	728[d]	48.0	26.5	0.55
5	536[e]	70.0	47.5	0.68
6	731	27.5	8.5	0.31
7-IM	805	8.5	5.0	0.59
8-IM	383[f]	10.0	5.0	0.50
Mean	584	39.2	20.0	0.51
Noon				
9	701[g]	40.0	23.5	0.59
10	848	163.5	44.5	0.27
11	687	16.5	21.0	1.27
12	987	17.0	17.5	1.03
13	805	65.5	50.0	0.76
14	689	37.5	58.0	1.55
15-IM	1508	34.5	15.0	0.44
16-IM	652[h]	79.0	25.5	0.32
17-IM	548	71.5	30.0	0.42
Mean	825	58.3	31.7	0.54
Evening				
18	666[i]	118.0	43.0	0.36
19	900	46.0	40.5	0.88
20	1017[j]	161.5	34.5	0.21
21	1196	51.0	31.5	0.62
22	1108	32.5	27.0	0.83
23	914	34.0	12.5	0.37
24-IM	1083[k]	50.0	30.5	0.61
25-IM	1288	39.5	27.0	0.68
Mean	1022	66.6	30.8	0.46
Mean of all meals	811	54.8	27.7	0.50

IM Institutional meals.
[a] Calculated as technical DDT.
[b] Calculated as recrystallized DDE.
Amounts lost on analysis and not included in totals. [c] 140 grams. [d] 49 grams. [e] 42 grams. [f] 192 grams. [g] 471 grams. [h] 75 grams. [i] 193 grams. [j] 268 grams. [k] 51 grams.

Source: Walker et al. 1954.[115]

Walker et al. found that the U.S. general population was chronically exposed to elevated levels of DDT, based on residues measured in normal meals in 1954—less than 10 years after the insecticide started being used as a pesticide throughout the nation. Although Walker et al. stated that the daily ingestion of 0.0026 DDT by an average man would not likeley produce systemic toxicity, they acknowledged that there was no precise toxicity information available for humans. Furthermore, they were solely focussed on sytemic toxicity or "injury":

> *To date there is no precise information as to the amount of DDT which can be consumed by humans over a long period of time wdthout the possibility of adverse*

> *results. Basing his conclusion mainly on chronic toxicity studies conducted on laboratory animals, but taking a safety factor into account, Neal (77) estimated that 5 mg. of DDT can be ingested daily without untoward effects… Fitzhugh (7) and Heyroth estimated that man can ingest 2.5 mg. of DDT daily over a long period of time without injury.*

However, they did not consider that even these low DDT exposures could cause DDT-induced cancer. Their summary completely ignored the study by Fitzhugh et al. (1947) that demonstrated DDT was carcinogenic. Fitzhugh et al. stated:

> *Taken together, the 15 rats having either liver tumor or nodular adenomatoid hyperplasia are numerically enough to strongly suggest a distinct although minimal tumorigenic tendency of DDT…The observations of this experiment show that chronic poisoning with small amounts of DDT is characterized by degenerative changes in the liver and other organs. This toxicity places a definite and inherent danger in the consumption of small amounts of DDT for a long time.*

In 1951, Laug et al. reported the presence of DDT in human breast milk.[116] They reported that, out of 32 women, "DDT was present in all except three of the specimens of human milk examined," with an average concentration of 0.13 ppm. In response to the amassed human studies, the American Medical Association (AMA) started speaking out regarding the dangers of bioaccumulating and biomagnifying DDT in human fat and the results of those high levels being detected in the U.S. population. In a 1951 editorial in the *Journal of the American Medical Association,* the AMA issued a warning about the potential consequences of the biomagnification of DDT.[117] Perhaps even more importantly, the editorial educated scientists and other health professionals for the first time about the critical function fat provides to health. In so doing, the AMA corrected many misconceptions—namely, that fat is just a depot or repository that holds fat like a "sponge." Most scientists at this time regarded fat tissue (known as *adipose tissue*) as a static nonmetabolic tissue that simply absorbed toxic lipophilic chemical compounds like DDT and PCBs. The AMA corrected this misconception by stating that adipose

tissue plays a vital role in many metabolic functions, and the accumulation of toxic lipophilic compounds could compromise health:

> *Adipose tissue is not merely connective tissue which functions in a passive manner as a fat depot; it is also a structure possessing functions that have been compared to those of a ductless gland… The tissue has a rich blood supply, and the mobilization and deposition of the fat is regulated by endocrine as well as nervous (sympathetic) influences… Nevertheless, enzymatic activity is carried out by the fat cells, which can accumulate glycogen, change carbohydrates into fat and transform one fatty acid into another. It has been asserted that, as part of the reticuloendothelial system, blood-forming functions may become established in adipose tissue under appropriate conditions, and that the cells of the omentum are capable of forming antibodies.*

As I noted in a previous section, the DDT stores are mobilized as part of the normal fat mobilization cycle of all adipose tissue, and the normal use of fat as an energy source releases "free" DDT that can then target different organs. DDT is also released in significant amounts in illness and disease—at precisely the time when further toxic insults can compound a person's illness. The AMA noted that normal fat turnover is continuous and that, although the human turnover rate is unknown, the turnover rate in the rat is just 6 days. This process can free up unbound DDT, which will then circulate in the blood:

> *The functions bearing directly on the mobilization and deposition of fat appear to be a continuous process. Complete fat turnover in the mouse on a constant diet is estimated to require six days. The turnover in man is probably slower, because his metabolic rate is lower; it most likely varies within wide limits and must be greatly accelerated under conditions that make demands on the fat reserve… It appears to be a reasonable assumption that adipose tissue, which has these many important functions, can be influenced by the presence of cumulative poisons such as the chlorinated hydrocarbon insecticides. Among the more important of these materials are dichlorodiphenyltrichloroethane (DDT)…"*

The AMA highlighted the fact that DDT is a proven "biological magnifier" with major implications because DDT continually builds up in adipose tissue and can insidiously target important cardiac enzymes and alter the metabolic activity of the adipose tissue itself:

> *The accumulation of dichlorodiphenyltrichloroethane in fat tissue has been studied extensively, and it has been shown that this tissue acts as a biologic magnifier for the insecticide. The ingestion of minute amounts of dichlorodiphenyltrichloroethane (about 1 part per million) in the diet of rats over a period of time causes accumulation in the fat which can be as high as 30 times the level of intake. It has been demonstrated that dichlorodiphenyltrichloroethane concentrations of 3 to 30 parts per million in the substrate inhibit rat heart cytochrome oxidase. It is possible that this deposited DDT can influence enzymatic activity in adipose tissue.*

The AMA also directly linked bioaccumulation to toxicity, stating that increasing lipid solubility increases toxicity:

> *Perhaps a better indication of the influence of a poison that is retained in the fat is the comparison of the effects of the four principal isomers of benzene hexachloride. If the degree or retention of gamma isomer in fatty tissue is assigned the value of 1, then alpha is rated as 2, beta as 10 and delta less than 1. Chronic effects of these isomers, when fed to rats, can be observed with 100 parts of gamma per million in the diet, 50 of alpha, 10 of beta and about 800 of delta. The direct relation between retention and chronic toxicity appears obvious.*

Additionally, the AMA highlighted an often-ignored fact about lipophilic chemical compounds. While scientists at this time had reached consesus that DDT bioaccumulation and biomagnifaction occurred in fat tissue, little thought had been given to the fact that every cell in the body has a membrane that is rich in lipids. When DDT dissolves in cell membranes, DDT can disrupt the very fine balance of cellular transport; transplacental transport in the developing fetus would be a major concern.

> *In fact, dichlorodiphenyltrichloroethane is found in all other tissues in proportion to their fat content. Fats and lipids are constituents of cell membranes and are concerned with the phenomena of cell permeability and cell organization in every tissue of the body…Also, embryonic fat cells have a great capacity for synthesis of cholesterol. The importance of cholesterol in the formation of vitamins and hormones is well established. Consequently, storage of a toxicant in the fat of parenchymal cells is essentially storage in the cell itself, where such important enzymatic processes as oxidation, phosphorylation and cholesterol synthesis take place. The fact that TDE specifically affects the adrenal cortex of the dog gives credence to this postulation.*

Finally, the AMA pointed to the properties of all lipid-soluble stable chlorinated hydrocarbons as the overriding threats to human health and the body's homeostatic mechanisms. In other words, the toxicity was not "chemical-specific," and if other compounds (such as PCBs) shared the physical property of fat solubility, they would be expected to be equally toxic.

> *At present, compounds of the chlorinated hydrocarbon group of insecticides that are fat soluble and chemically stable appear to be readily retained in adipose tissue. Such compounds possess a high order of chronic toxicity, and it is believed that at least part of these effects may be due to the adverse influence the chemicals have on important functions of adipose tissue.*

In 1955, a very important presentation was given at the AAAS meeting by Hayes et al. (the report was published in 1956) entitled, "The Effect of Known Repeated Oral Doses of Chlorophenothane (DDT) in Man."[118] Because previous animal studies had shown consistent but variable DDT bioaccumulation, Hayes et al. concluded it was necessary to confirm the effects of human exposures by directly exposing humans in a controlled feeding experiment and measuring DDT in biopsied fat tissue. This was a very unique set of experiments because humans were used as the "animal" and were knowingly exposed to a confirmed toxic compound:

> *Much knowledge is available regarding the effect of repeated doses of chlorophenothane (DDT) on a variety of animals. Significant interspecies variation has been found in its toxicity when given orally, the storage of DDT in fat, and the conversion of DDT to 1,1,-dichloro-2,2-bis(p-chlorophenyl) ethylene (DDE). Some other aspects of the pharmacology of DDT have not been investigated sufficiently to determine whether interspecies differences are present. A final evaluation of the effect of DDT on man must be made with human subjects. The practical importance of the problem is evident from the fact that a greater tonnage of DDT than of any other insecticide is used in agriculture, that DDT occurs regularly in prepared meals, and that it is stored in the fat of most persons in the general population.*

They stated that DDT was then known to have bioaccumulated "in most of the persons in the general population." This statement is extremely important and noteworthy for this case because Hayes et al. predicted bioaccumulation based on just two facts: 1) DDT's high lipid solubility had resulted in rapid and high bioaccumulation animals and livestock; and 2) a great "tonnage" of DDT had been released into the environment. Despite having no more information than these two facts, Hayes et al. felt comfortable about this prediction that the "general population" had accumulated DDT.

The Hayes et al. experiments[118][8] (started in 1954) were conducted on human male prison volunteers in which each man was given a daily dose of 3.5 or 35 mg DDT in various emulsions for periods of up to 18 months. At the end of the prescribed interval of an exposure, a small incision was made in the abdomen, a biopsy specimen of abdominal fat was removed, and the DDT content was measured. As noted earlier, the U.S. food supply was known to be contaminated, so adjustments were made for both DDT and DDE residue concencentrations detected in the typical prison meal.

Based on their graphs, Hayes et al. stated, "It is clear that storage was directly proportional to dosage. The graphs suggest that, at the dosages used, human males achieve storage equilibrium for DDT in about a year, but further observation is necessary to establish this." DDT had

bioaccumulated to significant levels even at low levels of exposure and that it was biomagnified. For example a DDT dose of 3.5 mg resulted in fat concentrations of 354 mg and 613 mg after approximately 6- and 12-month exposures, respectively. As the apex receptor in the food chain, humans unknowingly accumulate chlorinated compounds released into the environment to significant levels.

8.4. In the 1960s, DDT and PCBs were known to be ubiquitous and bioaccumulative

If PCBs had been substituted for DDT by investigators in each of the above-summarized studies, the results would have been roughly the same. As producers of both PCBs and DDT, Monsanto must have known that both compounds shared very similar lipid solubility properties and, therefore, should have known that all of the DDT studies pertained to PCBs as well. This proposition is supported by the testimony of Monsanto's corporate representative.[18]

By the 1960s, the full realization of the massive historical uncontrolled releases of both DDT and PCBs came into sharp focus. Detailed food residue measurements were made of these two highly lipid-soluble compounds in different categories of food products, confirming that the U.S. food supply was highly contaminated and that the general public had likely been unknowingly consuming DDT and PCBs for many years prior. Starting in 1969, the FDA began monitoring PCBs in a variety of foods and could then determine the amount of PCBs in the total U.S. diet; from this information, FDA could calculate the daily human PCB intake.[119]

In 1975, at the National Conference on Polychlorinated Biphenyls (sponsored by the U.S. EPA), Drs. Jelinek and Corneliussen (Director of the Division of Chemical Technology, Bureau of Foods, Food and Drug Administration and Assistant to the Director of the Division of Chemical Technology, Bureau of Foods, respectively) presented "Levels of PCBs in The U.S. Food Supply."[119]

[18] Kaley Deposition, Colella v. Monsanto, 11/17/2011, pages 34-44.

From the amount of PCB contamination measured in each food commodity, the authors calculated the average daily intake for a typical diet, which they termed the "Total Diet." It should be stressed that 50% of this population would have higher daily intakes. Jelinek and Corneliussen noted that they could look at the multiyear survey results and identify patterns of foods contaminated with the highest levels of PCBs and make the following broad generalization by 1975:

> *In summary, the breadth of occurrence of PCB's has narrowed to the point where freshwater fish are now the primary source of PCB's in our diet. Thus, the daily PCB intake for the average citizen is low, since his consumption of freshwater fish is low, and even here, most of the commercial freshwater fish contain less than 5 ppm PCBs. However, the estimated intake of the average consumer is only a guidepost, and the Food and Drug Administration must consider the dietary consumption patterns of significant sectors of the population which are significantly different from the average. For example, PCB intake could be quite different for those people whose diets include substantial quantities of sports fish.*

Because fish was the food commodity exhibiting the highest PCB contaminant levels, Jelinek and Corneliussen stated that the focus should be on preventing PCBs from entering and contaminating the aquatic environment:

> *For the future…means must be employed by the responsible Federal and State agencies to effectively halt the entry of PCB's into the aquatic environment.*

It wasn't until the early 1970s that routine biomonitoring of the U.S. general population was conducted to determine the body burdens for many environmental pollutants among the U.S. general population. In 1967, the Human Monitoring Survey was established by the Pesticides Program of the U.S. Department of Health, Education, and Welfare. In 1970, (the first year the EPA was established as an Agency), EPA began measuring DDT and, later in 1972, PCBs in fat tissue as part of its National Human Monitoring program. In these early biomonitoring studies, both DDT and PCBs were detected in the general population.[120]

Although the extent of PCB contamination was not widely studied until the late 1960s and 1970s, it is my opinion that Monsanto had all the facts necessary to know PCBs as bioaccumulative, ubiquitous environmental contaminants much earlier. This opinion is supported by a memo developed by a consultant (Dr. Robert Metcalf) for Monsanto in 1969.[121] At the time, Metcalf was a professor at Illinois University and one of Monsanto's scientific consultants. In 1969, he wrote an internal memo to Monsanto titled, "Report and Comments on Meeting on Chlorinated Biphenyls in the Environment at Industrial Biotest Laboratories, Chicago, March 21." In this memo, he considered whether it is possible that the massive amounts of PCBs Monsanto had produced over decades could have resulted in worldwide pollution. His conclusion was a simple yes. What is striking about Metcalf's conclusion is that it was based on a few specific long-known facts and scientific principles: Monsanto produced massive amounts of PCB over 40 years; tens of millions of pounds of PCBs were used in applications where PCBs "must escape into the environment;" PCBs are stable and environmentally persistent; and both PCBs and DDT are lipid soluble and water insoluble, and had been produced in roughly the same amounts over decades. Metcalf's conclusions did not require the development of any new technology or scientific discoveries—the stated bases for his conclusions were available to Monsanto decades before.

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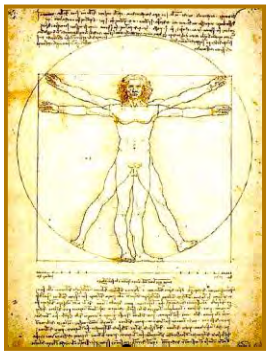

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DR. RICHARD L. DEGRANDCHAMP
President and Principal Toxicologist

EDUCATION

University of Colorado Medical School, Department of Physiology, National Institutes of Health Postdoctoral Fellow, 1988-1991

Rutgers University School of Pharmacy and Toxicology, Rutgers Postdoctoral Fellow, 1986-1988

Cornell University Medical School, Department of Pharmacology, Research Associate, 1987-1988

University of Michigan, School of Public Health, Ph.D., Toxicology, 1986

Eastern Michigan University, B.S., Biochemistry, 1978

ACADEMIC APPOINTMENTS

University of Colorado Denver/Anschutz Medical Campus, Faculty Member in Graduate Program
- Courses: Environmental Risk Assessment (2006-Current)
- Environmental Epidemiology (2008-Current)
- Toxicology (2016-Current)

University of Colorado Medical School, School of Pharmacy, Adjoint Professor
- Course: Risk Assessment and Toxicology (May 1998-2009)

Naval Civil Engineer Corps Officers School, Port Hueneme, California
- Courses: Human Health Risk Assessment and Management (1996-2002)
- Environmental Statistics (1996-2002)

PROFESSIONAL POSITIONS

Scientia Veritas, L.L.P.
Evergreen, Colorado
President and Principal Toxicologist
March 1997-Current

Terranext
Lakewood, Colorado
Corporate Director of Medical Toxicology and Health Sciences and Principal Toxicologist

November 1996-March 1997
GeoTrans Inc.
Boulder, Colorado
Director of Toxicology and Risk Assessment and Principal Toxicologist
February 1996-November 1996

PRC Environmental Management Inc.
Denver, Colorado
Toxicology and Atmospheric Science Discipline Leader and Principal Toxicologist
February 1992-November 1995

PTI Inc.
Boulder, Colorado
Senior Toxicologist
May 1991-February 1992

EPA Neurotoxicology Division
Research Triangle Park, North Carolina
Consulting Toxicologist
1984-1986

University of Michigan School of Public Health, Department of Industrial and Environmental Health
Ann Arbor, Michigan
Consulting Toxicologist and Research Assistant
1980-1986

University of Michigan School of Public Health, Department of Water Quality
Ann Arbor, Michigan
1978-1980
Research Assistant

PROFESSIONAL SOCIETIES/ASSOCIATIONS

Society of Toxicology
Society for Risk Analysis
Society of Environmental Toxicology and Chemistry
American Society for the Advancement of Science
American Chemical Society

PROFESSIONAL EXPERIENCE

EXPERTISE OVERVIEW

Dr. Richard DeGrandchamp has been a practicing toxicologist for more than 33years. During this time, he has served in the U.S. Department of Justice's (DOJ) Expert Witness Unit and testified in numerous high-profile trials involving environmental contamination in which the judgment awards totaled more than $20 billion. Dr. DeGrandchamp provides expert witness testimony to DOJ on risk assessment, chemical injury, and toxicology. He has also testified as the toxicologist

expert witness in numerous toxic tort lawsuits that focused on cancer-causing environmental toxicants. He has held a faculty appointment in the Graduate Faculty Program at the University of Colorado Denver/Anschutz Medical Campus for more than 15 years. Dr. DeGrandchamp has served on numerous scientific review panels and has been a toxicological consultant for the U.S. Environmental Protection Agency (U.S. EPA); Department of the Navy (DON); Department of Energy (DOE); Department of Defense (DOD); Massachusetts Department of Environmental Protection (MDEP); Michigan Department of Environmental Quality (MDEQ); District of Columbia's District Department of the Environment (DDOE); and many chemical, pharmaceutical, and manufacturing companies. He has conducted or directed more than 300 human health risk assessments regulated under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA; Superfund); Resource Conservation and Recovery Act (RCRA); and Underground Storage Tank (UST) programs. He has been the lead negotiator in over 150 regulatory meetings and provides expert toxicological support, as well as expert witness testimony, on all issues related to toxic chemical exposure. Dr. DeGrandchamp has provided expert toxicological legal support in the private sector and U.S EPA Regions 3, 5 and 8 in environmental cases involving RCRA and CERCLA hazardous sites. He has been a member of numerous expert scientific panels and authored many risk assessment, statistical, and toxicological guidance documents for U.S. EPA and DOD.

FACULTY APPOINTMENTS

Dr. DeGrandchamp holds a faculty appointment in the Graduate Program at the University of Colorado Denver/Anschutz Medical Campus where he is the lecturer and course director for three courses: Human Health Risk Assessment, Toxicology, and Environmental Epidemiology for the M.S. and Ph.D. program.

Dr. DeGrandchamp also taught human health risk assessment and toxicology courses at the University of Colorado Medical School, School of Pharmacy, where he was responsible for training students in the Ph.D. Toxicology Program.

Dr. DeGrandchamp was a faculty member and instructor at the Naval Civil Engineering Corps Officers School (CECOS), Port Hueneme, California. He developed the first courses for human health risk assessment, toxicology, and risk management.

Dr. DeGrandchamp has developed and presented a hands-on training, three-day toxicology/risk assessment workshop to risk assessors, physicians, and industrial hygienists at the Navy Environmental Health Center (NEHC), Bureau of Medicine, in Norfolk, Virginia.

Dr. DeGrandchamp has instructed many U.S. EPA CERCLA and RCRA personnel, and Navy project managers, in the practice and application of risk assessment, statistics, and toxicology at petroleum-contaminated sites.

LITIGATION EXPERTISE

Dr. DeGrandchamp has been retained as an expert toxicologist to evaluate the cause of death of a 14 male adult. This individual suffered acute and severe clonic-toxic seizures triggered by numerous prescribed medications to control his seizures Dr. DeGrandchamp is investigating the cause of death. He has been tasked with evaluating the toxicity and synergistic effects of the prescribed medications by the attending physician and how the nursing personnel administered the drugs. He is also determining if his non-prescribed drugs that led to his emergency admission could have contributed to his death and he is reviewing all medical records and hospital treatment to determine and explain the how the child died.

Dr. DeGrandchamp has been retained as toxicological expert consultant for a case involving a pesticide (pyrethroid) exposure that resulted in a 6th month old infant developing severe tonic clonic seizures. He was asked to provide a review of the available medical toxicology information for the pesticide as well as the patient medical records to form an opinion about whether the medical treatment he received during his hospitalization the prescribed medications were correctly administered. He has been tasked with identifying the initial triggering cause and the subsequent toxicological sequelae that

have now triggered nearly 1,000 seizures per day and resulted in severe impairment of cognitive development.

Dr. DeGrandchamp has been retained as an expert for a case involving PFAS contamination and exposure to residents. He will be testifying on all issues relating to PFAS toxicity and epidemiology studies in a large cohort (approximately 30,000 residents) that have been exposed to PFAS over the last 4 decades.

Dr. DeGrandchamp has been retained as an expert for a PCB case involving contaminated fish. He will be testifying on all issues relating to the human health risks and toxicology of PCB ingestion at different transects of a major river that encompasses areas of fishing.

Dr. DeGrandchamp has been retained as an expert for a polluted site where PFAS was manufactured and have been released into a river that serves as a drinking water source for hundreds of thousands of residents. This group of toxic chemical compounds includes PFOA, PFOS, as well as more recently manufactured compounds that were specifically developed to replace the highly toxic PFAS compounds (including GenX, and Nafion-117) that are no longer produced in the U.S. He has been tasked with forming an opinion about the individual and collective toxicity of these compounds to the exposed population. He is responsible for reviewing company documents that include operation history and numerous toxicity studies.

Dr. DeGrandchamp is an expert witness for a toxic-tort lawsuit. He will be testifying that decades of exposure to PCBs caused diverse and severe health effects in a tribe that was exposed to PCBs over 4 decades. He is responsible for evaluating the fingerprint from multiple sources and linking those to blood samples for the cohort. He will be evaluating specific PCB congeners based on body burden studies and show they are specifically associated with non-cancer health effects based on a series of epidemiology studies. He will also be conducting an epidemiology study of cancers in the cohort to determine if those PCBs are also associated with an elevated risk of cancer.

Dr. DeGrandchamp is an expert witness for a coal-burning facility that has generated numerous heavy metals that have contaminated numerous properties near the facility. He is responsible for evaluating the regional distribution of centrospheres, that serve as indicator particles, to first identify the extent of the regional contamination and then to evaluate the heavy metal contamination associated with those particles to determine if the level of those metals pose a risk to the community.

Dr. DeGrandchamp is an expert witness for a PCB site, where PCBs have been historically released for more than four decades to determine the sources of those PCBs as a foundation to identify localized releases of Potentially Responsible Parties. He will be determining the extent of regional Natural Resources damages for purposes of liability and to support extensive cleanup.

Dr. DeGrandchamp recently completed testifying in a series of toxic tort lawsuits suits that culminated in a jury award of $46 million for three Non-Hodgkin Lymphoma (NHL) patients. During these trials, his testimony on the history of cancer testing demonstrated Monsanto could have and should have conducted cancer studies back in the 1930s and that those studies would have clearly shown PCBs were carcinogenic, which could have prevented widespread PCB environmental contamination that then ultimately led to contamination of the U.S. food supply over an 80-year period. He showed that while hundreds of other synthetic chemicals resembling PCBs had been tested for carcinogenicity by 1940, Monsanto took no steps to conduct any cancer study until the 1960s. He also provided testimony that linked PCB-body burden with NHL, which was necessary to prove Monsanto's PCBs "caused" NHL. For this part of his testimony, Dr. DeGrandchamp showed that the complex molecular events triggered by PCBs cause specific genetic lesions at locations in the DNA, triggering a cascade of events that result in NHL (summary available at http://verdictsearch.com/verdict/monsanto-to-blame-for-pcb-exposure-cancer-suit-argued/; http://www.ecowatch.com/monsanto-ordered-to-pay-46-5-million-in-pcb-lawsuit-in-rare-win-for-pl-1891143419.html). This verdict subsequently triggered settlement discussions (reported to be $280 million) that are underway between the hundreds of remaining NHL patients and Monsanto.

Dr. DeGrandchamp is the expert witness for plaintiffs in the Blackwell Zinc Smelter lawsuit alleging property damages due to lead, arsenic, and cadmium contamination of more than 200 properties in Blackwell, Oklahoma. He is responsible

for conducting risk assessments to determine the effects of contaminants on the central nervous systems of the Blackwell children living on contaminated Blackwell properties.

Dr. DeGrandchamp was the DOJ expert in toxicology in the British Petroleum (BP) Deep Water Horizon oil spill in the Gulf of Mexico case that was settled last year for $20 billion (case summary available at: https://www.justice.gov/enrd/deepwater-horizon). He was responsible for conducting toxicological evaluations, epidemiology studies, and risk assessment to assess the potential health threats to more than 40,000 cleanup workers and shoreline residents living in Louisiana, Florida, and Alabama.

Dr. DeGrandchamp was the expert consultant to the U.S. Department of Justice providing toxicology and risk assessment support on a coke/steel manufacturing operation site in West Virginia. He was responsible for assessing human health risks to children living off site in a residential area and at their schools. He determined that the cancer and noncancer risks were unacceptable based on recent EPA air monitoring data collected at nearby schools. Dr. DeGrandchamp applied EPA guidance for early lifetime exposures for coke-related contaminants that are mutagenic. He also conducted an epidemiological evaluation and determined that the residential population was at risk for a wide range of medical conditions.

Dr. DeGrandchamp was an expert consultant to DOJ on the Centredale Manor Superfund site in Rhode Island. This complex site was highly contaminated with dioxins, PCBs, and heavy metals. DOJ was awarded $104 million, and a case summary is available at https://www.epa.gov/enforcement/case-summary-epa-issues-104-million-order-cleanup-work-centredale-manor-superfund-site.

Dr. DeGrandchamp was retained as an expert witness in a toxic tort suit involving a wrongful death associated with exposure to cleaning solutions. He was responsible for evaluating all medical records and the death certificate to determine whether the cause of death was related to an acute exposure.

Dr. DeGrandchamp was an expert witness for the District of Columbia's Department of the Environment and D.C. Attorney General's office in a case involving vapor intrusion into approximately 500 homes in Washington D.C. due to gasoline and chlorinated solvents (PERC). For this site, he conducted more than 1,500 individual risk assessments for each of the sites to identify specific homes where the contaminants could trigger medical conditions and/or cancer and made the necessary toxicological/dosimetric adjustments to EPA toxicity values for early life exposures and individuals with preexisting medical conditions. This study was used to determine which homes required vapor mitigation to reduce indoor contaminants to acceptable levels. Dr. DeGrandchamp also conducted a newly developed forensic statistical approach to determine the responsible contaminant sources.

Dr. DeGrandchamp served as the toxicological expert for the Navy Office of General Council and the Navy Environmental Health Center, Bureau of Medicine, in a toxic tort suit filed by more than 6,000 residents on the Island of Vieques. He evaluated the plaintiffs' claims alleging long-term toxic exposures due to Navy activities on the island over a 60-year period associated with bombing exercises resulted in wide-ranging medical conditions. Damages were set at more than $1 billion. Dr. DeGrandchamp was responsible for analyzing hundreds of historical documents, medical records, and biological hair samples. Additionally, he was responsible for analyzing biological samples to determine the current levels of toxic metal exposures to distinguish between background and military-related exposures, as well as conducting an epidemiological study to verify cancer rates, which were then compared with the current cancer registry.

Dr. DeGrandchamp was an expert witness providing toxicological expertise to DOJ and EPA Region 3 on the Metal Bank Superfund Site in Pennsylvania, which was contaminated with PCBs and dioxins. He provided expert reports, rebuttal reports, supplemental reports, depositions, and interrogatories, and assisted DOJ in preparing for depositions. Ultimately, the court ruled in DOJ's favor, deferring to Dr. DeGrandchamp's expert opinion regarding the level of contamination and associated human health risks. He also provided supporting risk assessments in the second phase of the trial, where he developed a risk-based remedial strategy for mitigating risks to acceptable levels. A summary of the approximate $30 million settlement is available at https://www.paed.uscourts.gov/documents/opinions/03D0023P.pdf

Dr. DeGrandchamp was an expert witness for DOJ in a bankruptcy trial for three hazardous waste sites in Pennsylvania. He

was responsible for conducting a toxicological assessment of potential risk associated with exposure to PCBs and to address the question of whether it was necessary to secure the funds for future remediation. The court ruled for DOJ and required that $15 million be secured for additional studies and remediation.

Dr. DeGrandchamp was an expert witness for DOJ and EPA Region 8 involving PCBs and dioxins at the U.S. Magnesium Corporation (MagCorp) Superfund Site in Utah. He was responsible for conducting a comprehensive toxicological evaluation of workers' health and exposure conditions based on their occupational responsibilities within the plant. He collaborated with Occupational Safety and Health Administration (OSHA), National Institute for Occupational Safety and Health (NIOSH), and EPA toxicologists and physicians to design and implement a medical surveillance program in which blood samples and employee coveralls were collected to determine the extent of dioxin and PCB exposure. Based on the blood sample data, Dr. DeGrandchamp was able to identify high-risk workers and submit a worker protection plan to attenuate exposures. He also used the dioxin levels measured in their contaminated work coveralls to show they were exposing family members to high cancer risk and reproductive effects. This analysis proved that they were unknowingly engaging in the well-known phenomenon of "Fouling Their Own Nests" and provided the basis for developing a worker and family protection plan.

Dr. DeGrandchamp served as the expert toxicologist for U.S. DOJ and U.S. EPA Region 5 in a case against a steel manufacturing facility in Ohio. He was responsible for conducting toxicological evaluations for residents who lived near the AK Steel Superfund Site and had been eating PCB-contaminated fish caught in a nearby river. Upon completion of expert reports, a settlement was reached for approximately $25 million. A description is available at https://www.justice.gov/archive/opa/pr/2006/April/06_enrd_200.html.

Dr. DeGrandchamp has provided expert testimony in several toxic tort litigation cases for a potentially responsible party at a chrome-plating facility in Texas. His responsibilities included reviewing medical records, preparing pretrial reports, giving depositions, presentations during arbitration and mediations, and preparing guardian *ad litem* documents.

Dr. DeGrandchamp has worked extensively with U.S. Navy attorneys on diverse health and environmental issues. Dr. DeGrandchamp provided toxicological expertise and negotiation support in the Navy CLEAN program. He was a member of a multifaceted installation wide technical panel that evaluated the legal basis for developing innovative remediation strategies to streamline the CERCLA process for all Navy bases scheduled for closure or transfer. He prepared position papers; developed the Navy's overall remediation strategy; and negotiated with local, state, and federal regulatory agencies. He was the technical expert in numerous negotiations and dispute resolution meetings.

Dr. DeGrandchamp served as the toxicological expert in a toxic tort case filed against a major pesticide manufacturer that involved domestic exposure to a pyrethroid pesticide. He prepared an expert report that was successfully used to have the case dismissed.

Dr. DeGrandchamp provided litigation support for a toxic tort case involving a PRP in Montana involving exposure to petroleum constituents. His responsibilities included developing the overall scientific strategy and designing a sampling plan for the defense.

Dr. DeGrandchamp provided legal support for a chlorinated solvent site in Montana. He also served as the technical advisor on community relations for this project. He was responsible for interacting with the U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR).

SUMMARY OF PROJECT EXPERIENCE

Under Dr. DeGrandchamp's direction, SV was awarded a sole source contract to provide expert consulting services to the Michigan Department of Environmental Quality (MDEQ). Dr. DeGrandchamp provided toxicological, risk assessment, and negotiation support to MDEQ regarding perfluorinated chemical (PFCs) contamination of Wurtsmith Air Force Base groundwater that migrated offsite to the Au Sable River, where it has contaminated fish. Dr. DeGrandchamp conducted a literature review of PFC information; prepared a report summarizing findings of the literature search; conducted a site-

specific review and analysis of PFC data from the Wurtsmith site; performed a comparison of exposure and general media contaminant levels at other sites (nationally and worldwide); analyzed the potential risks to humans and ecosystems in and around the Wurtsmith site; provided a report on the site-specific review and analysis; provided an analysis of Air Force responsibilities in relation to CERCLA and other environmental and human health regulations; proposed additional work at the Wurtsmith site by the Air Force, MDEQ, and/or EPA necessary to identify risks, actual human health impacts and ecological impacts, as appropriate; summarized this analysis into a report of additional responsibilities; and traveled to Michigan to meet with personnel from MDEQ and the Air Force.

The PFCs are the result of firefighting training activities at Wurtsmith, and Dr. DeGrandchamp provided support to MDEQ in working with EPA Region 5 and the U.S. Air Force. PFCs constitute an emerging group of highly toxic chemicals of concern (COCs) and Dr. DeGrandchamp was charged with developing toxicity values. SV was also contracted to work on the project because of Dr. DeGrandchamp's previous experience working on Air Force projects. Dr. DeGrandchamp aided the state of Michigan in connecting with the proper Air Force personnel in order to secure funding for future studies and in pointing out to all parties the benefits of conducting such work before any potential property transfers or re-use plans are implemented.

Under Dr. DeGrandchamp's direction, SV was awarded a sole source contract with the District of Columbia Department of the Environment and is currently providing oversight for all risk assessments at the Washington Navy Yard in D.C., which has been in continuous operation for 200 years. He is responsible for evaluating the public health threats from contaminants on the base, as well as releases into the Anacostia River. He is currently conducting a forensic analysis of PCBs and dioxins that will be used to forensically "fingerprint" different sources of contamination in the river.

Dr. DeGrandchamp conducted a time-critical toxicological evaluation of children in a daycare facility in the District of Columbia that resulted in an emergency evacuation of children from the daycare. His analysis showed vapor levels had reached neurotoxic levels, which required evacuation until vapor mitigation systems could be installed.

Dr. DeGrandchamp prepared toxicological support for new regulations for exposure to toxic chemicals bacteria, viruses, and protozoa in stormwater reuse in D.C. The approach combines the risk assessment approach developed by U.S. EPA and the World Health Organization's disability-adjusted lifetime years (DALY).

Dr. DeGrandchamp was retained to provide expert witness testimony in a toxic tort suit involving a death from phosphoric acid inhalation. Responsibilities included evaluating epidemiological/toxicological published studies to derive the plausible lethal dose, reconstructing possible exposure dose, reviewing medical records to evaluate etiology of illness and symptoms leading to death, and a critique of the coroner's report.

Dr. DeGrandchamp has developed new toxicity values for DON for chemicals did not have U.S. EPA-verified toxicity values. To date, he has developed toxicity values for more than 95 chemicals.

Dr. DeGrandchamp routinely conducts toxicological reviews to determine if U.S. EPA-toxicity values need to be modified or updated based on new toxicological studies.

Dr. DeGrandchamp prepared a comprehensive guidance document on sampling and analysis, and conducting risk assessments at PCB- and dioxin-contaminated sites for DOD. These documents were used to train Navy personnel in the environmental restoration program who are responsible for remediating Navy installations that will be returned to civilian use.

Dr. DeGrandchamp conducted a geostatistical analysis of background conditions for dioxin, furans, and PCBs for the Rocky Mountain Front Range for EPA Region 8. This analysis was based on a new statistical method he developed based on geochemical analyses using linear regression and principal component analysis.

Dr. DeGrandchamp developed and negotiated a geochemical method for evaluating background conditions in the state of Florida for the Department of Defense (Navy). After conducting a pilot study to demonstrate that the geochemical technique could be used to define background conditions and identify chemical release areas, the Florida Department of Environmental Protection (FDEP) formally approved the technique for use on Superfund and Federal Facilities throughout Florida.

Dr. DeGrandchamp conducted a toxicological evaluation of chemicals detected at Naval Air Station (NAS) Atsugi in Japan for the Department of the Navy. This project involved developing new toxicity values for unique chemicals and their breakdown products. This was a sole source contract resulting from specific recommendations by the National Academy of Sciences and the Navy Surgeon General. Ultimately, Dr. DeGrandchamp used these toxicity values to show that contaminant levels did not pose risks to Japanese citizens.

Dr. DeGrandchamp was selected by U.S. EPA to serve on an expert External Peer Review Panel to provide technical oversight for *Draft Human Health Risk Assessment Protocols for Hazardous Waste Combustion Facilities and Screening Level Ecological Risk Assessment Protocols for Hazardous Waste Combustion Facilities.* He was responsible for providing expertise in risk assessment and toxicology on the panel and participated in a two-day public hearing/workshop to field and respond to public comments prior to finalization and release of the guidance.

Dr. DeGrandchamp served as the Technical Lead for EPA Region 6 in developing a new technical guidance document for RCRA sites: *Risk Management Strategy.* He was responsible for all technical sections and responding to public comments.

Dr. DeGrandchamp served as an Expert Consultant to Booz Allen for a project involving asbestos-containing materials (ACMs) at Lowry AFB in Colorado. His responsibilities included researching technical and legal precedence for sampling ACM in soil; reviewing Air Force ACM sampling work plans for substance and approach; identifying potential legal liabilities pertaining to ACM issues; outlining ACM health risk scenarios; and recommending a path forward for ACM sampling and remedial activities for the Air Force at Lowry AFB, Colorado. In the course of this work, Dr. DeGrandchamp conducted surveys and pattern analysis of surface soil; attended meetings/negotiations with CDPHE; provided legal non-testifying expert support to Air Force attorneys; developed sampling and analysis plans for contaminated areas and activity-based sampling; conducted statistical analysis on areas of concern; developed risk management protocols and evaluated several novel approaches based on new analytical procedures to expedite decision-making; conducted field investigations; reviewed extensive epidemiological studies to evaluate toxicological endpoints; and calculated health risks and prepared risk assessment reports.

Dr. DeGrandchamp provided EPA Region 8 with toxicological and risk assessment technical support at two RCRA sites involving hazardous solvent exposure to off-site residents. He was responsible for evaluating risks and health hazards associated with vapor entering homes from contaminated groundwater into nearby homes. He was responsible for evaluating current toxicological peer-reviewed toxicological studies on formaldehyde to identify health problems among residents, determine acceptable levels of exposure, and identify homes that may require interim measures or evacuation of residents.

Dr. DeGrandchamp conducted a background analysis implementing *Procedural Guidance for Statistically Analyzing Environmental Background Data,* which he authored for the Navy, at NAS Whiting (Milton Florida). This approach was then used to identify chemicals of concern for risk assessment, evaluate Applicable or Relevant and Appropriate Requirements (ARAR), and identify chemical releases. Successful completion of this project was expected to save DOD and the state of Florida $30 million in potential remediation costs.

Dr. DeGrandchamp conducted a comprehensive review and analysis of diverse scientific methods used to evaluate risks associated with lead exposure for DON. He prepared a Navy position paper that evaluated all lead risk assessment models, including the scientific veracity of the U.S. EPA Integrated Exposure Uptake Biokinetic Model (IEUBK) software code, the California Lead Spread Model, and the probabilistic Integrated Stochastic Model to make recommendations for improvement. He also developed the DON risk assessment strategy to evaluate adult lead exposure in order to expedite lead cleanup at closing Naval installations.

Dr. DeGrandchamp developed a cost-effective, risk-based corrective action (RBCA) approach for a hazardous waste site for Lockheed Martin in Denver, Colorado. The approach incorporated Monte Carlo simulation techniques to accurately estimate actual site-specific risks based on realistic exposures. A cost-benefit matrix was developed to guide risk management decisions.

Dr. DeGrandchamp provided technical expertise on wide-ranging issues to EPA Regions 8 and 6 RCRA and CERCLA programs. He provided toxicological and statistical support on all remedial investigations and feasibility studies conducted

at Rocky Flats Nuclear Weapons Plant (RFP) and was involved in all investigations pertaining to the analysis of human health risks resulting from chemical and radionuclide exposures. He developed data quality objectives and risk assessment methodology, statistical analyses, sampling and analysis plans, and oversaw all chemical and radiological fate and transport modeling. He compiled a database for conducting Monte Carlo simulations and provided technical reviews on supplemental guidance for conducting Monte Carlo simulations for EPA Region 8. He developed a cost-effective risk assessment template for RFP to streamline and provide consistency for all risk assessments. Dr. DeGrandchamp was responsible for evaluating DOE's statistical analyses and risk assessments, and ensured results were consistent with U.S. EPA, the International Commission on Radiation Protection (ICRP), and Nuclear Regulatory Commission (NRC) methodologies. He assisted EPA Region 8 in negotiating numerous disputes and was a participant in a workgroup of nationally recognized experts in binding arbitration involving statistical analyses. He was selected as a member of an interagency committee that included the Colorado Department of Natural Resources, Colorado Department of Health, Colorado Fish and Wildlife Service, EPA Region 8, and DOE to scope, design, and implement a comprehensive, installationwide human health and ecological risk assessment for Rocky Flats.

Dr. DeGrandchamp provided scientific expertise to DOE on toxicological, risk assessment, and statistical issues at the Savannah River Site (SRS) in South Carolina. He reviewed human health risk and dose assessments conducted for numerous operable units and participated on a task force responsible for establishing background conditions. He was invited to lecture on risk assessment and statistical issues by EPA Region 4, DOE, and the South Carolina Department of Health project managers and toxicologists.

Dr. DeGrandchamp conducted numerous baseline risk assessments at NAS Lemoore in California. These risk assessments were ultimately combined into a comprehensive installationwide risk assessment that involved fate and transport modeling of contaminants, coupled with the analysis of current and potential future health risks. He was responsible for all negotiations with federal and state regulators. He successfully negotiated cost-effective management of human health risks during remedy selection by using a risk-based approach to avoid unnecessary and expensive remediation.

Dr. DeGrandchamp conducted all risk assessments and coordinated feasibility studies for NAS Moffett Field in California. He carried out a detailed future land use analysis that was used to focus risk mitigation strategies based on probable future land use. The land use analysis was also used to focus human health risk assessments on realistic exposure conditions to avoid unrealistic conservative default assumptions. He negotiated all aspects of the risk assessment approach with state and federal regulatory agencies. The Navy requested that Dr. DeGrandchamp assist the Department of Justice in averting formal dispute resolution.

Dr. DeGrandchamp conducted risk assessments for NAS Alameda in California. He was responsible for developing the overall risk assessment approach and negotiating all technical aspects of the Navy project with local, state, and federal regulators. He was also tasked with preparing innovative approaches to establish anthropogenic and nonanthropogenic background conditions, preliminary remediation goals, and data aggregation to estimate exposure-point chemical doses. He was also responsible for developing a Navy policy document for risk-based corrective action at petroleum sites.

Dr. DeGrandchamp provided oversight to DOD for risk assessments conducted for NAS China Lake. He was responsible for implementing a risk-based, cost-effective approach for remediation and alternative cleanup levels based on actual site exposures.

Dr. DeGrandchamp provided technical expertise to the Massachusetts Department of Environmental Protection for radionuclide risk assessments, compliance, and cleanup standards. He worked with the state to develop state guidance for radionuclide cleanup of all Department of Defense and Nuclear Regulatory Commission operated sites within the state.

Dr. DeGrandchamp provided EPA Region 8 with technical oversight for all remedial investigations and risk assessments for F.E. Warren Air Force Base in Wyoming and Tooele Army Depot in Utah. He conducted a risk assessment in response to an emergency exposure condition for off-site residents at F.E. Warren AFB who were directly exposed to high concentrations of organic solvents.

Dr. DeGrandchamp led the human health and environmental risk assessment task force for EPA Region 6 in studying

potential adverse health effects associated with emissions from several incinerators in Midlothian, Texas. This investigation was prompted by strong public concern about adverse health effects on humans and livestock. In this evaluation, Dr. DeGrandchamp analyzed the potential for dioxin to produce birth defects, spontaneous abortions, and other potential toxic effects.

Dr. DeGrandchamp investigated the human health risks associated with RCRA facilities in southern California. He conducted the risk assessment for the onsite human receptors, as well as the surrounding community, to determine the potential risks to pregnant women from benzene, arsenic, and cadmium exposure in groundwater. He also evaluated the risks to fetuses via *in utero* exposure. At another RCRA facility, he conducted a risk analysis to determine potential risks associated with arsenic-laden fly ash used as landfill material.

Dr. DeGrandchamp provided oversight and technical support to the EPA Region 8 (Montana office) RCRA division for remediation of oil refineries in Billings, Montana; Mandan, North Dakota; and Commerce City, Colorado. He oversaw all phases of the RCRA process involving preliminary investigations and corrective measures studies. He developed health-protective cleanup levels, and evaluated facility permitting and remediation enforcement. Together with Colorado Department of Health officials, he worked to negotiate remediation goals and a cost settlement.

BIOMEDICAL RESEARCH

Dr. DeGrandchamp investigated the neurotoxic mechanisms associated with exposure to mercury and acrylamide. This information was incorporated into the toxicological database developed by U.S. EPA and the Occupational Safety and Health Administration to set regulations and establish safe exposure conditions for occupational workers.

Dr. DeGrandchamp investigated the neurotoxic effects of alcohol on the developing nervous system, which produces fetal alcohol syndrome. He was responsible for developing new research methodologies and approaches to investigate subtle molecular changes in the nervous system.

Dr. DeGrandchamp designed experimental paradigms to study the bioavailability of mineralogical forms of heavy metals, such as arsenic and cadmium, from mining tailings for a CERCLA site in Montana.

Dr. DeGrandchamp worked on a project for the National Institutes of Health to investigate the neurophysiological mechanisms of strychnine poisoning. In this capacity, he coordinated a team of experts and managed all technical personnel in a multifaceted research program to elucidate the steps that result in central nervous system damage.

Dr. DeGrandchamp further refined the neurotoxic esterase *in vivo* enzyme assay used to evaluate neurotoxic damage resulting from nerve agents and pesticides. This laboratory method has become a standard methodology to screen neurotoxic compounds in the chemical industry and to evaluate the neurotoxic potential of chemical weapons. He also developed a correlative animal model for U.S. EPA to quantify chemical-induced neuropathies associated with exposure to pesticides and nerve agents.

PUBLICATIONS AND POLICY DOCUMENTS

Dr. DeGrandchamp has authored over 100 major toxicological and human health risk assessments that have undergone extensive peer-review. However, many of these reports could not be published due to confidentiality or proprietary information.

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effects of chronic perinatal ethanol exposure. *Proc. of the Society of Physiology.* Washington, DC: Society of Physiology.

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APPENDIX B: MILESTONES IN CANCER STUDIES PERTAINING TO PCBs

1775: First Environmental Cancer Identified
Dr. Percivall Pott identifies a relationship between exposure to chimney soot and the incidence of squamous cell carcinoma of the scrotum among chimney sweeps. This later established the connection between coal tar carcinogens and cancer. His report is the first to clearly link an environmental exposure to the development of cancer, as described in Casarett and Doull. [2]

1798: US Public Health Service Established
Fifth Congress of the United States creates agency that later became the US Public Health Service (US PHS) in 1912. The agency is now known as the US Department of Health, Education and Welfare (https://www.usphs.gov/aboutus/history.aspx). [3]

1863 Inflammation and Cancer
Dr. Rudolph Virchow identifies white blood cells (leukocytes) in cancerous tissue, making the first connection between inflammation and cancer. Virchow also coins the term *leukemia* and is the first person to describe the excess number of white blood cells in the blood of patients with this disease. PCBs cause immunotoxicity (https://www.cancer.gov/research/progress/250-years-milestones). [4]

1889 Mitotic Figures Identified in Tumors
Dr. Klebs first identifies mitotic figures in tumors (Triolo 1965). [5]

1899 Hyaline Bodies Identified as Cancer Hallmarks in Liver Cancer
Dr. Keen reported his findings of hyaline bodies in liver cells from a tumor mass he removed from a patient. (Triolo 1965). [5]

1906 Pure Strains of Laboratory Rats Developed
Wistar Institute Breeds Wistar Rat Strain for Biomedical Studies (Baker et al. 1979). [1]

1915: Additional Strains of Laboratory Rats Developed
Long-Evans Rat strain developed for biomedical studies (Baker et al. 1979). [5]

1915 First Carcinogenic Chemical Animal Study
Drs. Yamagiwa and Itchikawa induce skin cancer in rabbits by painting coal tar on their ears, constituting the first experimental animal cancer study. Coal tars provide the starting chemical compounds for chemical industry (Loeb and Harris 2008). [6]

1922 First Governmental Cancer Research Center Opens
US Public Health Service establishes a special cancer investigations laboratory at Harvard Medical School (https://www.usphs.gov/aboutus/history.aspx). [2]

1925 Extensive Pathological "Atlas," Hallmarks of Cancer Described
Dr. Ludford publishes a lengthy treatise titled, The general and experimental cytology of cancer. The pathological lesions used to identify cancers and establishes mitotic figures as key hallmarks of cancer (Ludford 1925). [7]

1925 Last Major Strain of Laboratory Rats Developed Sprague-Dawley Rats bred for laboratory research (Baker et al. 1979). [5]

1934 Dow Chemical Company Establishes its Toxicology Laboratory [8]

1934 Monsanto Begins Testing for Acute PCB Toxicity
Monsanto toxicity studies determine how much can kill animals and evaluates the acute toxic effects of PCBs. Monsanto does not evaluate chronic toxicity in any study until 1970, when the first long-term rat study is completed (Appendix C).

1935 Drs. Sasaki and Yoshida Report on Yoshida's First Long-Term Animal Cancer Study
Liver tumors were produced in rats by including azo dyes in their diets, as reported by Sasaki and Yoshida (in German, 1935), and then by Loeb and Harris. [6]

1935 DuPont Dedicates the Haskell Laboratory
The laboratory was built to conduct toxicity studies to protect the health of workers from toxic new chemical products during their manufacture, as well as public health. Laboratories were designed for biochemistry, pathology, and toxicology, and the laboratory was completed with a full library for studying toxicological problems (JAMA 1935). [9] The stated goal was to "Test Each Product for Safety." [8]

1936 U.S. Public Health Service Recommends Chlorinated Hydrocarbon Manufacturing Be Entirely Enclosed and Recommends Laws Be Passed for Medical Monitoring
Dr. Schwartz, MD, a Senior Surgeon in the U.S. Public Health Service, published a peer-reviewed study detailing the emerging reports of widespread skin diseases

and systemic toxicity among workers who were exposed to chlorinated compounds, including PCBs. He made eight specific recommendations to protect both workers and the general public from exposures (Schwartz 1936). [9]

1937 Mitotic Figures Are Now Routinely in Animal Cancer Studies and Clinical Practice To Identify Tumors

Dr. Casey publishes a study showing that counting the number of mitotic figures in tumors was so established and routine that clinical pathologists and oncologists based their diagnoses and prognoses on this one cancer hallmark. (Casey 1937)

1937 National Cancer Institute created by US Congress

Congress passed the National Cancer Act of 1937 to support for cancer research. The Act established the National Cancer Institute (NCI) as the federal government's primary agency to address research and training needs for the cause, diagnosis, and treatment of cancer (https://www.cancer.gov/about-nci/overview/history). [10]

1938: DuPont Publishes First Animal Cancer Study

Dr. Hueper identifies DuPont chemicals (not known to be human carcinogens) based on chemical structural triggers in animal studies and identifies many that are carcinogenic. Hueper identifies additional DuPont chemical candidates based on triggers focusing on structural similarities (Hueper 1938). [11]

1937 First PCB Study Published

Dr. Drinker et al. study shows PCBs are extremely toxic and produce unique pathological lesions in the liver (Drinker et *al.,* 1937). [12]

1938 First Major List of Animal Cancer Studies Published

Drs. Cook and Kennaway publish summaries of chemicals tested for carcinogenicity in chronic animal studies, listing approximately 170 referenced studies (Cook and Kennaway 1938). [12]

1938 Second Study on PCBs Published

Dr. Bennett et al. showed unique pathological lesions in the livers of rats that were caused by PCBs. Hyaline bodies, mitotic figures, and hyperplasia were reported, which are all early hallmarks of cancer. [14]

1938 Dow Chemical Company Completes First Long-Term Animal Carcinogenicity Study [15]

1939 Workplace Exposure PCB Levels Developed

Dr. Drinker et al. published further observations on the possible systemic toxicity of certain of the chlorinated hydrocarbons, with suggestions for permissible concentrations in the air of workrooms (Drinker et al. 1939). [16]

1940 Second Major List of Animal Cancer Studies Published
Drs. Cook and Kennaway publish second list of chemicals tested for carcinogenicity in chronic animal studies. The publication lists approximately 480 referenced studies (Cook and Kennaway 1940). [12]

1941 Dr. Berenblum First Describes the Molecular Mechanism of Cancer
Cancer studies have advanced to study the mechanism of carcinogenesis using coal tar chemicals. [18]

1941 National Cancer Institute Compiles Extensive Compendium of Chemicals Tested in Animal Studies
This summarizes the results of 696 of animal studies focusing on diverse chemicals, identifies 169 carcinogenic chemicals, and includes 1200 references. [19]

1944 First Commercial Pure Aroclor Toxicity Study [21]

1955 U.S. Public Health Service Publishes Review of the Toxicity of PCBs
Dr. von Oettingen, previously DuPont's first director of the Haskell Laboratories and now the director of the National Institutes of Health, US Department of Health, Education, and Welfare, reviewed the same Drinker studies that I have analyzed and presented his assessment of the toxicity and dangers of PCBs in a book he authored, The Halogenated Hydrocarbons: Toxicity and Potential Dangers. Dr. von Oettingen concluded that PCBs were very toxic and were much more toxic than chlorinated naphthalenes. [21]

1966 Widespread PCB Contamination Identified in Sweden
Dr. Jensen reports on widespread PCB contamination in the environment. [22]

1968 Yusho Massive PCBs Poisoning in Japan from 1788 People Eating PCB Contaminated Rice
A mass poisoning incident, was caused by ingestion of rice oil that was contaminated with Kanechlor 400, a commercial brand of Japanese PCBs and also contaminated with polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs). Of the 31 deaths reported, 11 (35.5%) were from neoplasms. Among the Yu-Cheng patients, 24 deaths were reported; half of them were from hepatoma, liver cirrhosis, or liver diseases with hepatomegaly. [24]

1970 Monsanto Completes Its First Chronic PCB Study in Rats
The study was conducted by Industrial Bio-Test Laboratories (IBT) and purports to show that PCBs are not carcinogenic, but the studies do not appear to be credible. In reviewing past contract testing work performed by IBT to evaluate the large disparity between IBT's results and other published PCB cancer studies, three IBT scientists were convicted of submitting fraudulent studies to the US

Food and Drug Administration (FDA) in 1993. One of the animal toxicity studies was performed on Monsanto's trichlorocarbanilide ("TCC"), an ingredient in deodorant soaps. (https://www.courtlistener.com/opinion/460360/united-states-v-moreno-l-keplinger-paul-l-wright-and-james-b-plank/). IBT prepared three allegedly fraudulent written documents that Monsanto submitted to the FDA. [23]

APPENDIX C: SUMMARY OF MONSANTO

PRODUCT TESTING, 1934-1972

Exhibit C-1. Chemical Structure Categories: Polychlorinated Biphenyls and Similar Compounds

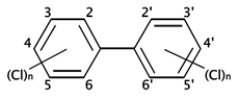
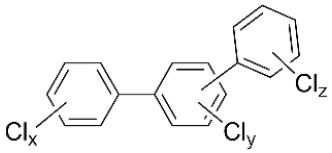
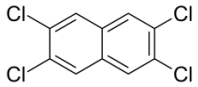
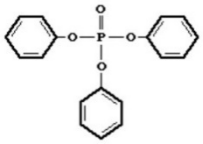
Compound	Chemical Structure
Polychlorinated biphenyls	
Polychlorinated terphenyls	
Polychlorinated naphthalenes	
Pydraul	

Exhibit C-2. Number of Studies Provided by Monsanto, by Category and Specific Chemical

Chemical Category	Number of Studies
Aroclors	
Aroclor 1016	1
Aroclor 1221	8
Aroclor 1232	1
Aroclor 1242	20
Aroclor 1248	4
Aroclor 1254	17
Aroclor 1260	15
Aroclor 1262	3
Aroclor 1268	2
Aroclor 1269	1
Aroclor 1272	1
MCS 1016	6
Total Studies on Chemicals in Category	**79**
Monsanto Mixtures (Not Pure Biphenyl PCBs)	
5-ring polyphenyl ether product	2
Aroclor 1270 ammonia reaction product	1
Aroclor 2565	1
Aroclor 4273	1
Aroclor 4465	2
Aroclor 5432	1
Aroclor 5442	2
Aroclor 5460	4
Aroclor 6037	1
Aroclor 6040	1
Aroclor 6062	1
Aroclor 6070	1
Aroclor 6090	1
Aroclor Mixture Aroclor/Styrene	3
Aroclor/Halowax Mixtures	4
Chloro Ethyl Benzene	1

Chemical Category	Number of Studies
Chlorinated Styrene	1
DDT	4
FH 145	1
FH-159	1
Inerteen PPO	1
Halowax 1000 (chlorinated naphthalenes)	1
Halowax 1001	1
Halowax 1004	1
Halowax 1014	2
Halowax 1099	3
Hydrolyzed Aroclor 1268	1
MCS-1009	1
MCS-1230	1
MCS-153	1
MCS-295	1
MCS-312	1
MCS-300	1
MCS-395	1
MCS-404	2
MCS-528	2
MCS-90	1
MCS-900	1
MCS-9001	1
MCS-999	1
OS-54	1
OS-57	1
OS-63	1
OS-83	1
OS-95	3
Pydraul	1
Pydraul 135	1
Pydraul 230	1
Pydraul 280	2
Pydraul 281	1
Pydraul 312	1
Pydraul 600	2
Pydraul 625	2
Pydraul AC	2

Chemical Category	Number of Studies
Pydraul F-9	5
Pyranol 1470	1
Santicizer 1706	1
Toxaphene	3
Tricresyl phosphate	1
Total Studies on Chemicals in Category	**86**
Manuscripts and Memos Not Considered a Study	
Not a study	6
Total Reports in Category *(not included in total)*	**6**
Total	**165**

Exhibit C-3. Toxicological Analysis
Studies Conducted by Monsanto Contractors (1934–1972)

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
1. 1934 (0001) REPORT OF DR. FREDERICK B, FLINN OF PATCH TESTS MADE ON MATERIAL RECEIVED FROM SWANN RESEARCH, INC. Dr. Frederick Flynn	Acute dermal patch study with rabbits. Endpoint - dermatitis with short 24 or 48 hr. exposures and 8 tests per solution. 2 week observation.	1. Aroclor 1262: Neg. Rxn. 2. Aroclor Mixture Aroclor/Styrene: Neg. Rxn. 3. Aroclor Mixture: Aroclors/Styrene: Pos. Rxn 4. Aroclor 1248: Pos. Rxn 5. Aroclor 1248 "Special": Pos. Rxn. 6.Aroclor 1269: Neg. Rxn. 7. Aroclor Mixture: Aroclor/Styrene Neg. Rxn. 8. Aroclor 1269: Neg. Rxn. 9. Aroclor 1269: Neg Rxn. 10. Halowax 1000(chlorinated naphthalenes) : Pos. Rxn with ulceration. 11. Halowax 1001: Neg. Rxn. 12. Halowax 1004: Neg Rxn. 13. Styrene Dichloride: Pos. Rxn. 14. Aroclor 1248: Pos. Rxn . 15. Aroclor 1260: Neg. Rxn. 16. Aroclor 1262: Neg. Rxn. 17. Chlor Ethyl Benzene: Pos Rxn./Ulceration 18. Chlorinated Styrene: Pos Rxn/Ulceration
2. 1937 (0005) THE PROBLEM OF POSSIBLE SYSTEMIC EFFECTS FROM CERTAIN CHLORINATED HYDROCARBONS. Drs. Drinker, Field, Bennett	Discussed in Section 2.	Aroclor/Halowax Mixtures
3. 1938 (0034) MORPHOLOGICAL CHANGES IN THE LIVERS OF RATS RESULTING FROM EXPOSURE TO CERTAIN CHLORINATED HYDROCARBONS. Drs. Bennett, Drinker, Warren	Discussed in Section 2.	Aroclor/Halowax Mixtures
4. 1938 (0061) REPORT TO THE MONSANTO CHEMICAL COMPANY. Dr. Drinker.	Discussed in Section 2.	Aroclor/Halowax Mixtures

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
5. 1938 (0061) REPORT TO THE MONSANTO CHEMICAL COMPANY. Dr. Drinker. Second Report Same Year	Discussed in Section 2.	Not a study. Aroclor/Halowax Mixtures
6. 1938 REPORT TO THE MONSANTO CHEMICAL COMPANY Dr. Drinker.	Discussed in Section 2.	Not a Study. Aroclor/Halowax Mixtures
7. 1939 (0085) FURTHER OBSERVATIONS ON THE POSSIBLE SYSTEMIC TOXICITY OF CERTAIN OF THE CHLORINATED HYDROCARBONS WITH SUGGESTIONS FOR PERMISSIBLE CONCENTRATIONS IN THE AIR OF WORKROOMS. Dr. Drinker	Discussed in Section 2.	Aroclor/Halowax Mixtures
8. 1948 (0091) COVER LETTER: PROJECT W-31 AROCLOR (REPORT ON PATCH TESTING) Dr. Halpern The Barnard Free Skin and Cancer Hospital. One Page	Human screening "Patch Test" Simple test to evaluate if "Aroclors" irritated the skin or caused sensitization from contact with Aroclors. Raw data and details not presented-nevertheless irritation was considered negative. Cohort: 46 volunteers aged 20-53 yrs old 36F/10M ("no negros") . Protocol was very short-term. 24 hr exposure and observed for 48,72 hours for irritation. Repeated 10 days later for "sensitivity."	Not a Study. One-page summary did not identify specific Aroclor. Skin irritation.
9. 1949 (0092) COVER LETTER: PROJECT W-31 AROCLOR (REPORT ON PATCH TESTING) Dr. Halpern, The Barnard Free Skin and Cancer Hospital. Two Pages	Appears to be similar to the study referenced above (1948) with larger cohort (218 v. 46) volunteers. Cohort: 218 aged 20-70 yrs 131F/87M Protocol was very short-term. 24 hr exposure and observed for 48,72 hours for irritation. Repeated 10 days later for sensitivity.	Handwritten note states the Aroclor tested was "1254".

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
10. 1951 (0094) THE MINIMUM LETHAL DOSE OF PYDRAUL F-9 WHEN FED ORALLY TO NEW ZEALAND WHITE RABBITS. Fred Younger, Scientific Associates	Single Minimum Lethal Dose (MLD) study. Determined the acute toxicity from one single high dose. MLD was 0.45–0.67 ml/kg body weight (rabbit) . Interesting that although Aroclors were had been manufactured at this point for ~19 years Monsanto did not conduct a similar MLD study on that group.	Pydraul F-9: Not pure Aroclor Organophosphate with 52.5% Aroclor 1248 added. Single Minimum Lethal Dose (MLD) study. Determined the acute toxicity from one single high dose of Pydraul F-9. The MLD would be classified as very toxic. Death was used as an endpoint and only gross observations of organs were made during necropsy.
11. 1951 (0096) THE MINIMUM LETHAL DOSE OF PYDRAUL F-9 WHEN FED ORALLY TO LABORATORY RATS. Fred Younger, Scientific Associates	Single Minimum Lethal Dose (MLD) study. Determined the acute toxicity from one single high dose. MLD (rat) was 8.4–12.5 ml/kg body weight. This dose is more than 10x higher than previous study with rabbits. One of the key findings was the rats showed severe jaundice with liver damage.	Pydraul F-9: Not pure Aroclor Organophosphate with 52.5% Aroclor 1248 added. Single Minimum Lethal Dose (MLD) study. Determined the acute toxicity from one single high dose of Pydraul F-P MLD was 0.45 and 0.67 ml/kg body weight. Interesting that although Aroclors were had been manufactured at this point for ~19 years Monsanto did not conduct a similar MLD study on that group.
12. 1951 (0098) Letter report to Dr. Kelly from Dr. Halpern, The Barnard Free Skin and Cancer Hospital. Report is illegible, but appears to be a patch test for Pydraul F-9.	Report was illegible.	Pydraul F-9 (?)
13. 1953 (0100) THE TOXICITY OF THE FOGS FORMED BY DROPPING PYDRAUL F-9, AROCLOR 1248 AND TRICRESYL PHOSPHATE, UPON THE SURFACE OF A HEATED INCONEL (PROJECT 49) . Treon, Cleveland, Shaffer, Cappel, Gahegan, Wagner. Kettering Laboratory, University of Cincinnati.	Short term (acute) study of the effects of inhalation when vaporized on inconel tubes heated to extreme conditions. Exposure to Aroclor 1248 caused fatty infiltration and necrosis of liver parenchymal cells. Animals survived exposure to Pydraul F-9 and tricresyl phosphate, but died with Aroclor 1248. Significant differences in toxicological effects between species. Toxic effects were dose related. Skin patch tests were also conducted and showed a dose-dependence mortality ratio of all compounds. MLD of undiluted Pydraul F-9, when maintained in contact with the intact skin of rabbits according to the 24-hr sleeve method of Draise, Woodard and Calvery, was > 3.6 ml/kg and <6.0 ml/kg body weight. Correspond value for tricresyl phosphate was 1.6–2.5 ml/kg. Aroclor 1248 was not lethal at 9.4 ml/kg. Pydraul F-9 and Aroclor 1248 are more toxic if applied to the abraded skin.	Pydraul F-9: Not pure Aroclor: Organophosphate with 52.5% Aroclor 1248 added. Toxicity of Pydraul F-9, “Fogs.” Effects on lung, and liver evaluated. Patch tests also conducted.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
14. 1953 (0182) THE ACUTE ORAL TOXICITY (LD50) OF AROCLOR 1254 FOR RATS. Fred Younger, Scientific Associates.	The purpose of the study was to determine the lethal dose of Aroclor 1254 based on the LD50. It is noteworthy that the "LD50" toxicity test was developed by Bliss in 1939, but Monsanto did not conduct this very basic toxicity study until 1953 which is >20 years after production and use started. The LD50 was determined to be 3.1 ml/kg (rat) .	Aroclor 1254 was used to kill rats. The endpoint was mortality. No cause of death was investigated. Only gross observation was conducted at necropsy. Color change of liver was noted.
15. 1953 (0185) THE ACUTE ORAL TOXICITY (LD50) OF AROCLOR 1242 FOR RATS. Fred Younger, Scientific Associates.	The purpose of the study was to determine the lethal dose of Aroclor 1242 based on the LD50. It is noteworthy that the "LD50" toxicity test was developed by Bliss in 1939, but Monsanto did not conduct this very basic toxicity study until 1953 which is >20 years after production and use started. The LD50 was determined to be 4.15 ml/kg (rat) .	Aroclor 1242 was used to kill rats. The endpoint was mortality. No cause of death was investigated. Only gross observation was conducted at necropsy. Color change of liver was noted-dull red greenish hue. Spleen abnormally dark.
16. 1954 (0188) (A) THE ACUTE ORAL TOXICITY (LD50) OF FUNCTIONAL FLUID OS-54 FOR RATS (B) INHALATION OF OS-54 FUMES BY RABBITS OVER PERIOD OF THREE DAYS (C) OCULAR IRRITATION PRODUCED BY OS-54 Fred Younger, Scientific Associates	Acute (LD50) study to determine the lethal dose, eye irritation and inhalation toxicity. Acute oral toxicity (rat) : the LD50 was 13.5 g/kg.	Copy was illegible, but appears to reference OS-54. OS designation appears to indicate it is an aromatic ether not Pure Aroclor
17. 1954 (0194) THE TOXICOLOGICAL INVESTIGATION OF FLUID OS-57 Fred Younger, Scientific Associates	Acute oral LD50, dermal lethal dose, eye and skin irritation and inhalation toxicity. The LD50 (rat) could not be determined but highest dose was 28.5 g/kg. Overall toxicity very low.	OS-57 Handwritten note indicates study was with Pydraul 150. Not Pure Aroclor Organophosphate with 52.5% Aroclor 1248 added. I THINK THIS WAS COPIED. NOT SURE IT IS CORRECT.
18. 1955 (0200) TOXICOLOGICAL INVESTIGATION OF PYDRAUL F-9 (FH-103). Fred Younger, Scientific Associates	The oral LD50 (rat) was 24 g/kg. Skin absorption MLD (rabbit): 2.0–2.8 g/kg. Low dermal and eye irritation. why the lethal dose was greater with dermal absorption than oral administration.	Pydraul F-9: Organophosphate with 52.5% Aroclor 1248 added. Animals were exposed to Pydraul F-9 and acute toxicity evaluated with oral, eye and skin exposures.
19. 1955 (0206) Toxicological investigation of Fluid OS-63 Fred Younger, Scientific Associates	The oral LD50 (rat) was 17 g/kg. Skin absorption MLD (rabbit) : 2.4-3.0 g/kg Low dermal and eye irritation. Why the lethal dose was greater with dermal absorption than oral administration.	Animals were exposed to Fluid OS-63 and acute toxicity evaluated with oral, eye and skin exposures.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
20. June 22, 1955 (0212) THE TOXICITY OF THE VAPOR OF AROCLORS 1242 AND 1254. Treon, Cleveland, Shaffer, Cappel, Atchley, Torbeck, Wagner. Kettering Laboratory, University of Cincinnati.	Study results are invalidated due to the wide spread epidemic of pneumonia infection and ill health of colony of laboratory animals. Should not be considered a "toxicity" study since the majority of the "health" endpoints were death and body weight. Concludes that mortality was due to natural pneumonia infections not Aroclors. Authors state that although mortality rate was not increased: "For practical purposes this conclusion is subject to the critique of further experiments involving more prolonged exposure of animals to somewhat lower concentrations."	Aroclor 1242, 1254 inhalation study. Several endpoints measured but findings negated by poor health of animals.
21. June 28, 1955 (0314) THE TOXICITY OF THE VAPOR OF AROCLOR 1242 AND OF AROCLOR 1254. Treon, Cleveland, Shaffer, Cappel, Boller, Torbeck, Kettering Laboratory, University of Cincinnati.	Study was a supplement to earlier study. Results are largely invalid. There was wide spread epidemic of pneumonia infection and ill health of colony of laboratory animals. The mortality rate of all animals-including controls-was unacceptably high. States that there were no gross or microscopic evidence of pathology with Aroclor 1242 although Aroclor 1254 exposures produced lesions in livers and kidneys. Authors state that prolonged respiratory exposure to Aroclor 1254 is capable of causing some injury to the tissues of susceptible animals…	Not a study. Aroclor 1242, 1254
21. July 5 1955 (0388) THE TOXICITY OF A MIST GENERATED BY THE ASPIRATION OF PYDRAUL. Treon, Cleveland, Atchley. Kettering Laboratory, University of Cincinnati.	Specific purpose was to determine if Pydraul vapors produced during simulation of a catapult system on an aircraft carrier were toxic from an acute exposure. Following 2 or 4 hr. to 0.45 mg/L exposures guinea pigs died. Cats, rabbits, and rats survived; livers and kidneys were examined after sacrifice, and cats and rabbits exhibited degenerative changes.	Not pure Aroclor. Specific type of Pydraul; organophosphate/aroclor added not identified. Pydraul is not pure Aroclor. Endpoint was death.
22. 1955 (0404) TOXICOLOGICAL INVESTIGATION OF PYDRAUL 600. Fred Younger, Scientific Associates	Screening toxicity study for oral lethal dose and eye and skin irritation. Only gross observation of organs. No cause of death. Oral LD50 (rat) = 30.5 g/kg. Skin absorption MLD (rabbit) : 3.9–5.2 g/kg. Slight skin and eye irritation with Draize test. No deaths on vapor inhalation.	Pydraul 600. Not Pure Aroclor. Precise chemical composition not known, but Pydraul 625 is Organophosphate containing 50% Aroclor 1260.
23. 1955 (0410) TOXICOLOGICAL INVESTIGATION OF PYDRAUL 600. Fred Younger, Scientific Associates	Follow-up to previous study with single dose of 25.0 g/kg. Oral LD50 is ~0.72 g/kg for rabbits. The compound proved to be much more toxic for rabbits than for mice.	Pydraul 600. Not Pure Aroclor. Precise chemical composition not known, but Pydraul 625 is Organophosphate containing 50% Aroclor 1260.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
24. 1956 (0413) TOXICOLOGICAL INVESTIGATION OF PYDRAUL AC (OS-67) Fred Younger, Younger Laboratories	Screening Study for oral lethal dose, eye and skin irritation, and inhalation exposure Oral LD50 (rats) : 52 g/kg Oral MLD (rabbits) : 3.5–4.5 g/kg Skin Absorption MLD (rabbits) : 4.0–5.0 g/kg Slight skin and eye irritation with Draize test. Survived inhalation for 6 hours.	Pydraul AC: Not Pure Aroclor, 5-Ring Polyphenyl Ether organophosphate
25. 1957 (0420) TOXICOLOGICAL INVESTIGATION OF: HYDRAULIC FLUID OS-81- MONSANTO SAMPLE N0.1; HYDRAULIC FLUID OS-83 – MONSANTO SAMPLE NO.2 Fred Younger, Younger Laboratories	Screening Study for oral lethal dose, eye and skin irritation, and inhalation exposure OS-81: Oral LD50 (rat) : 8.6 g/kg Oral MLD (rabbit) : 0.35–0.5 g/kg Mild skin, eye, inhalation OS-83: Oral LD50 (rat) : 34.3 g/kg Oral MLD (rabbit) : 4.25–5.0 g/kg Mild skin, eye, inhalation	Aromatic Ether-Not Pure Aroclor
26. 1957 (0430) TOXICOLOGICAL INVESTIGATION OF AROCLOR 1270 AMMONIA REACTION PRODUCT Fred Younger, Younger Laboratories 3 Pages	Screening Study for oral lethal dose, eye and skin irritation exposure. Oral LD50 (rat) : 7.10 g/kg mild eye and skin irritation	Not Pure Aroclor. Aroclor 1270 Ammonia Reaction Product
27. 1958 (0433) TOXICOLOGICAL INVESTIGATION OF OS-95 Fred Younger, Younger Laboratories	Screening Study for oral lethal dose, eye and skin irritation exposure. Oral LD50 (rat) : 10.5 g/kg, Skin absorption MLD (rabbit) : 0.63–1.25 g/kg mild eye and skin irritation, and mild inhalation	Not Pure Aroclor. 5 Ring Polyphenyl Ether Product
28. 1958 (0440) THE TOXICITY OF THE THERMAL DECOMPOSITION PRODUCTS OF 'PYDRAUL 625' Fred Younger, Younger Laboratories	Rats were exposed to "fogs" of Pydraul that was superheated. Moderate mist 6hrs 2/8 deaths (18 and 21 days) . Heavy Mist 15 min. all rats survived. Heavy Mist 1hr. all survived	Pydraul 625. Not Pure Aroclor. Organophosphate containing 50% 1260. General observations of animals after exposures. Death was the endpoint

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
29. 1958 (0448) TOXICOLOGICAL INVESTIGATION OF THE FOLLOWING COMPOUNDS 1.POLYCHLORINATED BISPHENOL (HYDROLYZED AROCLOR 1268) , SAMPLE NO. 119; 2) DIGLYCIDYL ETHER OF TETRACHLOROBISPHENOL A (?) , SAMPLE NO 120; 3) DIGLYCIDYL ETHER OF POLYCHLORINATED BISPHENOL, SAMPLE NO. 121 REST OF TITLE AND TEXT MOSTLY ILLEGIBLE.	Single Dose Screening Study for oral and dermal lethal dose. 1.POLYCHLORINATED BISPHENOL (HYDROLYZED AROCLOR 1268), Oral LD50 (rat): 785 mg/kg Skin absorption lethal dose (rabbit) : >2.5 g/kg and <3.25 g/kg 2) DIGLYCIDYL ETHER OF TETRACHLOROBISPHENOL A (?) Oral LD50 (rat): 28.8 g/kg Skin absorption (rabbit) : highest application of 10 g/kg was nonlethal 3) DIGLYCIDYL ETHER OF POLYCHLORINATED BISPHENOL Oral LD50 (rat): 5.5 g/kg Skin absorption (rabbit): highest application of 10 g/kg was nonlethal All, non to mild eye and skin irritants	Not Pure Aroclor. Hydrolyzed Aroclor 1268.
30. 1958 (0463) TOXICOLOGICAL INVESTIGATION OF OS-95. Fred Younger, Younger Laboratories	Screening study for skin absorption and irritation. Sample 102, Lot 7501-3677 Skin absorption MLD (rabbit) : 2–2.5 g/kg Sample 17, Lot S-59 Skin absorption MLD (rabbit) : 1.25–1.5 g/kg Both, mild to moderate skin irritants.	Not Pure Aroclor. 5-Ring Polyphenyl Ether
31. 1958 (0467) THE TOXICITY OF THE THERMAL DECOMPOSITION PRODUCTS OF 'OS-95' Fred Younger, Younger Laboratories	Exposure to fog of thermal decomposition products. Moderate mist (6 h): no deaths Heavy conc (15 min): no deaths. Heavy conc (1 h): No deaths.	Not Pure Aroclor. 5-Ring Polyphenyl Ether
32. 1962 (0475) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1232. Fred Younger, Younger Laboratories.	Oral LD50 (rat) : 4.47 g/kg Skin absorption MLD (rabbit) : >1.26 g/kg and <2 g/kg	Aroclor 1232. Single dose skin irritation and death.
33. 1962 (0479) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1221. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 4.98 g/kg (slightly toxic) Skin absorption MLD (rabbit) : >2 g/kg and <3.16 g/kg (slightly)	Aroclor 1221. Single dose death skin irritation and death.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
34. 1962 (0483) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1242. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 8.65 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : >794 g/kg and < 1.26 g/kg (moderately toxic)	Aroclor 1242. Single dose death skin irritation and death.
35. 1962 (0487) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1248 Fred Younger, Younger Laboratories	Oral LD50 (rat) : 12.5 g/kg (practically nontoxic) Skin absorption MLD (rabbit) : >794 g/kg and <1.26 g/kg	Aroclor 1248
36. 1962 (0491) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1260. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 10 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : >1.26 g/kg and <2 g/kg (moderately toxic)	Aroclor 1260. Single dose skin irritation and death.
37. 1962 (0495) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1254. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 11.9 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : >1.26 g/kg and <2 g/kg (moderately toxic)	Aroclor 1254. Single dose skin irritation and death.
38. 1962 (0499) TOXICOLOGICAL INVESTIGATION OF AROCLOR: 1262. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 11.3 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : >1.26 g/kg and <3.16 g/kg (mildly toxic)	Aroclor 1262. Single dose skin irritation and death.
39. 1962 (0503) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 4465. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 16 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : > 2 g/kg and <3.16 g/kg (slightly toxic) Mild skin irritation, moderate eye irritant.	Not Pure Biphenyl Aroclor. Aroclor 4465: Terphenyl Single dose skin irritation and death.
40. 1962 (0509) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 1268. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 10.9 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : highest application = 2.51 g/kg (slightly toxic) Mild skin irritation, moderate eye irritant.	Aroclor 1268. Aroclor Single dose skin irritation and death.
41. 1962 (0513) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 2565. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal LD50 study. Oral LD50 (rat) : 6.31 g/kg (essentially nontoxic) Skin absorption MLD (rabbit) : >2 g/kg and <3.16 g/kg (slightly toxic) Mild skin irritation.	Not Pure Bi-phenyl Aroclor. Aroclor 2565: 25% Terphenyl and 75% Aroclor 1265. Single dose skin irritation and death.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
42. 1963 (0517) TOXICOLOGICAL INVESTIGATION OF: PYRAN0L 1470. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal MLD50 study. Oral LD50 (rat) : 2.25 g/kg (slightly toxic) Skin absorption MLD (rabbit) : >2 g/kg and <3.16 g/kg (slightly toxic) Moderate skin irritation, moderate eye irritant, slightly toxic with inhalation.	Pyranol 1470. Aroclor 1254 Electrical Grade. Single dose oral and dermal death and irritation.
43. 1963 (0525) TOXICOLOGICAL INVESTIGATION OF: INERTEEN PPO. Fred Younger, Younger Laboratories.	Single dose oral LD50 study and dermal MLD50 study. Oral LD50 (rat) : 2.37 g/kg (slightly toxic) Skin absorption MLD (rabbit) : >3.16 g/kg and <5.01 g/kg (slightly toxic) Moderate skin irritation, moderate eye irritant, slightly toxic with inhalation.	Inerteen PPO. Not pure Aroclor-Dilute product of PCBs and mineral oil. Acute death and irritation body surfaces.
44. 1963 (0533) SUBACUTE DERMAL TOXICITY OF AROCLOR 1248. Richard Palazzolo, Industrial Bio-Test Laboratories, Inc.	Subacute dermal exposure. Three test groups with 2 rabbits/group for 20 days evaluated 2 weeks later. Groups were 10,50, 100 mg/kg/day. End point was primarily skin irritation. 50% of 50 mg/kg/day and all 100 mg/kg/day died. LD 50 = 50 mg/kg/day LD 0.01 = 16.8 mg/kg/d LD 99.99 = 150 mg/kg/d Liver discoloration in 50 and 100 groups with moderate necrosis in 50. Animals that died were not examined.	Aroclor 1248. Primary interest was LD50 and skin irritation with subacute 20 day exposures
45. 1963 (0549) SUBACUTE DERMAL TOXICITY OF AROCLOR 1242. Richard Palazzolo, Industrial Bio-Test Laboratories, Inc.	Subacute dermal exposure. Three test groups with 2 rabbits/group for 20 days evaluated 2 weeks later. Groups were 50, 75, 100 mg/kg/day. End point was primarily skin irritation. 50% of 50 mg/kg/day and all 100 mg/kg/day died. LD 50 = 75 mg/kg/day LD 0.01 = 44 mg/kg/d LD 99.99 = 128 mg/kg/d Liver discoloration in 50 and 100 groups with moderate necrosis in 50. Animals that died were not examined.	Aroclor 1242. Primary interest was LD50 skin irritation with subacute 20 day exposures
46. 1963 (0566) SUBACUTE DERMAL TOXICITY OF AROCLOR 1268. Richard Palazzolo, Acute Toxicity Department, Industrial Bio-Test Laboratories, Inc.	Subacute dermal exposure. Four test groups with 2 rabbits/group for 20 days evaluated 2 weeks later. Groups were 500, 1000, 1500, and 2000 mg/kg/day. End point was primarily skin irritation. All animals in 1500 and 2000 mg/kg/day groups died. LD 50 = 1250 mg/kg/d LD 0.01 = 635 mg/kg/d LD 99.99 = 2450 mg/kg/d	Aroclor 1268. Primary interest was LD50 skin irritation with subacute 20 day exposures

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
	Moderate hepatic necrosis in Liver in two high dose groups. Animals that died were not examined.	
47. 1963 (0602) SUBACUTE DERMAL TOXICITY OF AROCLOR 1254. Richard Palazzolo, Acute Toxicity Department, Industrial Bio-Test Laboratories, Inc.	Subacute dermal exposure. Four test groups with 2 rabbits/group for 20 days evaluated 2 weeks later. Groups were 10, 50,100, 200 mg/kg/day. End point was primarily skin irritation. 50% of animals in 50 and 100 groups died; 100% of animals in 200 group died LD 50 = 75 mg/kg/day LD 0.01 = 6.2 mg/kg/d LD 99.99 = 915 mg/kg/d Moderate liver necrosis seen in 50 and 100 group. Animals that died were not examined.	Aroclor 1254. Primary interest was LD50 and skin irritation with subacute 20 day exposures
48. 1963 (0620) SUBACUTE DERMAL TOXICITY OF AROCLOR 4465. Richard Palazzolo, Acute Toxicity Department, Industrial Bio-Test Laboratories, Inc.	Subacute dermal exposure. Three test groups with 2 rabbits/group for 20 days evaluated 2 weeks later. Groups were 75, 150, 300 mg/kg/day. End point was primarily skin irritation. 50% of animals at 150, 100% died at 300 LD 50 = 150 mg/kg/day LD 0.01 = 76 mg/kg/d LD 99.99 = 300 mg/kg/d Hepatic cell necrosis and vacuolization with mononuclear white blood cell infiltration in 150 group. Animals that died were not examined.	Aroclor 4465 – Not a pure Aroclor biphenyl. 40% terphenyl and 65% Aroclor with 65% chlorine. Primary interest was dermal LD50 and skin irritation with subacute 20 day exposures
49. 1963 (0637) TOXICOLOGICAL INVESTIGATION OF: MCS-300. Fred Younger, Younger Laboratories.	Acute exposure study Rat oral LD50: 8.9 g/kg Rabbit skin absorption MLD: >3.98 g/kg and < 6.31 g/kg Rabbit Skin irritation - moderate Rabbit Eye irritation - mild Rat Vapor inhalation - nontoxic	MCS – 300. Not an Aroclor. Aromatic Ether.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
50. 1964 (0645) TOXICOLOGICAL INVESTIGATION OF: FH-145. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 6.68 g/kg Oral MLD (rabbit) : >1 g/kg and <1.58 g/kg Skin absorption MLD (rabbit) : >2.51 g/kg and <3.98 g/kg Rabbit Skin irritation - moderate Rabbit Eye irritation - mild Rat Vapor inhalation – slightly toxic.	FH 145-330 (?) – Does not appear to be an Aroclor.
51. 1964 (0654) TOXICOLOGICAL INVESTIGATION OF: MCS-295. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 4.2 g/kg Skin absorption MLD (rabbit) : >0.5 g/kg and <0.8 g/kg Rabbit Skin irritation - moderate Rabbit Eye irritation – moderate Rat Vapor inhalation – nontoxic.	MCS-295. Not a pure Aroclor. Aromatic Ether
52. 1964 (0662) TOXICOLOGICAL INVESTIGATION OF: FH 159. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 8.9 g/kg Skin absorption MLD (rabbit) : >1.5 g/kg and <2.61 (?) g/kg Rabbit Skin irritation - moderate Rabbit Eye irritation – moderate Rat Vapor inhalation – nontoxic.	FH-159 - Not a Pure Aroclor.
53. 1964 (0670) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 280. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 11.8 g/kg Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg Rabbit Skin irritation - moderate toxic Rabbit Eye irritation – moderate toxic Rat Vapor inhalation – mildly toxic	Pydraul 280. Not a Pure Aroclor. Organophosphate with PCB added.
54. 1964 (0678) TOXICOLOGICAL INVESTIGATION OF: MCS 312. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 6.5 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <3.16 g/kg Rabbit Skin irritation – slight skin irritant Rabbit Eye irritation – slight eye irritant Rat Vapor inhalation – practically nontoxic	MCS 312. Not an Aroclor. Aromatic Ether

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
55. 1966 (0686) TOXICOLOGICAL INVESTIGATION OF: MCS 395. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 4.6 g/kg Oral MLD (rabbit) : 1.6 g/kg Skin absorption MLD (rabbit) : >2.5 g/kg and <4.0 g/kg Rabbit Skin irritation – nonirritating Rabbit Eye irritation – slight irritant Rat Vapor inhalation – non-toxic	MCS 395. Not an Aroclor. Aromatic Ether
56. 1966 (0695) TOXICOLOGICAL INVESTIGATION OF: MCS-404. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 19.8 g/kg Oral MLD (rabbit) : 1.6 g/kg/day Skin absorption MLD (rabbit) : > 1.0 g/kg and <1.6 g/kg Rabbit Skin irritation – slight irritation Rabbit Eye irritation – slight toxic Rat Vapor inhalation – non-toxic	MCS-404. Not a pure Aroclor. Aromatic Ether
57. 1966 (0704) TOXICOLOGICAL INVESTIGATION OF: MCS 90. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 3.3 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <3.2 g/kg Rabbit Skin irritation – slight irritation Rabbit Eye irritation – moderate toxic Rat Vapor inhalation – non-toxic	MCS 90. Not a pure Aroclor. Aromatic Ether
58. 1966 (0712) TOXICOLOGICAL INVESTIGATION OF: MCS 528. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 8.4 g/kg Skin absorption MLD (rabbit) : > 0.79 g/kg and <1.26 g/kg	MCS 528. Not a pure Aroclor. Aromatic Ether
59. 1966 (0716) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL AC. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 18.9 g/kg Skin absorption MLD (rabbit) : > 0.79 g/kg and <1.26 g/kg	PYDRAUL AC. Not a pure Aroclor. Organophosphate 47% containing 57% Aroclor 1254.
60. 1966 (0720) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 280. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 8.4 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <3.16 g/kg Liver dehydration and discoloration.	PYDRAUL 280. Not a pure Aroclor. Organophosphate containing PCBs.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
61. 1966 (0724) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 135. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 4.2 g/kg g/kg/day Skin absorption MLD (rabbit) > 1.26 g/kg and <2.0 g/kg Liver dehydration and discoloration.	PYDRAUL 135. Not a pure Aroclor. Organophosphate containing 9.5% Aroclor 1232, 36.5% Aroclor 1242
62. 1966 (0728) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 625. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 20.7 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <3.16 g/kg Liver discoloration.	PYDRAUL 625. Not a pure Aroclor. Organophosphate containing 50% Aroclor 1260
63. 1966 (0732) TOXICOLOGICAL INVESTIGATION OF: MCS 404. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 15.0 g/kg Skin absorption MLD (rabbit) : > 1.26 g/kg and <2.0 g/kg	MCS 404. Chemical Composition Unknown.
64. 1966 (0736) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL F-9. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 11.2 g/kg Skin absorption MLD (rabbit) : > 0.5 g/kg and <0.8 g/kg	Pydraul F-9. Not a pure Aroclor. Organophosphate containing 52.5% Aroclor 1248
65. 1966 (0740) TOXICOLOGICAL INVESTIGATION OF: MCS 153. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 7.9 g/kg Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg	MCS-153. Chemical composition unknown.
66. 1967 (0744) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 230. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) :10.5 g/kg Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg Rabbit Skin irritation – slight irritation Rabbit Eye irritation – mild irritant Rat Vapor inhalation – non-toxic	PYDRAUL 230. Organophosphate containing 3.0 % Aroclor 1221, 54.7 Aroclor 1242
67. 1967 (0752) TOXICOLOGICAL INVESTIGATION OF: (XA-140) SANTICIZER 1706. Fred Younger, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 6.9 g/kg	SANTICIZER 1706 Chemical composition unknown

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
68. 1969 (0754) TOXICOLOGICAL INVESTIGATION OF: SANTOSAFE 300 (MCS-528) OR-116021. Melvin Birch, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 4.9 g/kg Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg Rabbit Skin irritation – mild irritation Rabbit Eye irritation – slight irritant	Santosafe 300. Chemical composition unknown
69. 1969 (0760) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 312 (MCS-312) OR-116021 Melvin Birch, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 5.3 g/kg Skin absorption MLD (rabbit) : > 3.2 g/kg and <5.0 g/kg Rabbit Skin irritation – mild irritation Rabbit Eye irritation – slight irritant	Pydraul 312. Organophosphate containing 47.3% Aroclor 1242.
70. 1969 (0766) 30-DAY TISSUE COLLECTION STUDY IN ALBINO RATS WITH AROCLORS BTL-AROCLOR II James Plank, Industrial Bio-Test Laboratories, Inc. Tissues Sent To: Dr. Hunt, Monsanto	Not A Toxicology Study IBT – Conducted the feeding. Animals were sacrificed and tissues were shipped to Monsanto. Monsanto conducted	Aroclor II. 1. Aroclor 1242 2. Aroclor 1254 3. Aroclor 1260 Not Biphenyl Aroclors - Terphenyls 4. Aroclor 5460 5. Halowax 1014 62% Cl 6. Halowax 1099 52% Cl Non Aroclors 7. Toxaphene 8. DDT
71. 1969 (0773) CHICKEN RESIDUE STUDIES ON AROCLORS AND VARIOUS OTHER MATERIALS BTL-AROCLOR Allen Wolvin, Industrial Bio-Test Laboratories, Inc. Tissues Sent To: Dr. Hunt, Monsanto	Two Phase 1. Determine LD50 2. 7-day feeding at 1/5 LD50 dose Results: Oral LD50 for 4 Aroclors, 2 Halowax materials, and DDT: > 10 g/kg TOXAPHENE oral LD50: 0.316 g/kg No Toxicity Data Presented	1. Aroclor 1242 2. Aroclor 1254 3. Aroclor 1260 Not Biphenyl Aroclors - Terphenyls 4. Aroclor 5460 5. Halowax 1014 62% Cl 6. Halowax 1099 52% Cl Non Aroclors 7. Toxaphene 8. DDT

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
72. 1969 (0789) TOXICOLOGICAL INVESTIGATION OF: MCS 900 Melvin Birch, Younger Laboratories.	Acute exposure study causing death. Oral LD50 (rat) : 1.3 g/kg/day Skin absorption MLD (rabbit) : > 7.9 g/kg Rabbit Skin irritation – mild irritation Rabbit Eye irritation – slight irritant Vapor inhalation Non-toxic	MCS 900 Chemical composition unknown.
73. 1969 (0798) FOUR-DAY FISH TOXICITY STUDIES ON SEVEN MATERIALS Carmen Mastri, Industrial Bio-Test Laboratories, Inc. Sent to: Mr. Wheeler, Hunt, Monsanto	Acute 4-Day exposure to Trout and Blue Gill to determine LC50 Trout LC50 (4-day, ppm) 1. Aroclor 1242: >100 ppm 2. Aroclor 1254: >100 ppm 3. Aroclor 1260: >100 ppm 4. Aroclor 5460: >100 ppm 5. Toxaphene: 0.008 ppm 6. DDT 0.0052 7. Halowax 1099: (10–100 ppm) Blue Gill LC50 (4-day, ppm) 1. Aroclor 1242: 0.66 ppm 2. Aroclor 1254: 0.66 ppm 3. Aroclor 1260: >100 ppm 4. Aroclor 5460: >100 ppm 5. Toxaphene: 0.0056 ppm 6. DDT: 0.0078 ppm 7. Halowax 1099: (>100 ppm) Parentheses indicate range-finding data	1. Aroclor 1242 2. Aroclor 1254 3. Aroclor 1260 Not Biphenyl Aroclors - Terphenyls 4. Aroclor 5460 5. Halowax 1099 52% Cl Non Aroclors 6. Toxaphene 7. DDT
74. 1969 (0832) TOXICOLOGICAL INVESTIGATION OF: MCS 9001 Melvin Birch, Younger Laboratories, Inc.	Acute exposure study causing death. Oral LD50 (rat) : 1.2 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <2.0 g/kg Rabbit Skin irritation – non irritating Rabbit Eye irritation – slight irritant Vapor inhalation slightly toxic	MCS 9001 Chemical composition unknown.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
75. 1970 (0840) TOXICOLOGICAL INVESTIGATION OF: PYDRAUL 281—Lot QL-42 Melvin Birch, Younger Laboratories, Inc.	Acute exposure study causing death. Oral LD50 (rat) : 10.4 g/kg Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg Rabbit Skin irritation – mild to moderate irritant Rabbit Eye irritation – mild irritant Vapor inhalation non toxic	PYDRAUL 281 Organophosphate containing unknown PCB composition.
76. 1970 (0848) TOXICOLOGICAL INVESTIGATION OF: MCS 1009 Melvin Birch, Younger Laboratories, Inc.	Acute exposure study causing death. Oral LD50 (rat) : 7.7 g/kg Skin absorption MLD (rabbit) : > 1.3 g/kg and <2.0 g/kg Rabbit Skin irritation – moderate irritating Rabbit Eye irritation – slight irritant Vapor inhalation non toxic	MCS 1009. Unknown composition.
77. 1970 (0856) TOXICOLOGICAL INVESTIGATION OF: MCS 999 Melvin Birch, Younger Laboratories, Inc.	Acute exposure study causing death. Oral LD50 (rat) : 11.8 g/kg Skin absorption MLD (rabbit) : >3.2 g/kg and <5.0 g/kg Rabbit Skin irritation –mild irritating Rabbit Eye irritation – slight irritant Vapor inhalation non toxic	MCS 999. Unknown composition.
78. 1970 (0864) TOXICITY, REPRODUCTION AND RESIDUE STUDY ON AROCLOR 1242, LOT #AK-255; AROCLOR 1254, LOT #AK-38; AROCLOR 1260, LOT #AK-3 IN WHITE LEGHORN CHICKENS James Stephens, Industrial Bio-Test Laboratories, Inc.		1. Aroclor 1242 2. Aroclor 1254 3. Aroclor 1260
79. 1970 (0950) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 6062—LOT QM 1304 Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Oral LD50 (rat) : 8.1 g/kg Skin absorption MLD (rabbit) : > 7.9 g/kg Rabbit Skin irritation –slight irritating Rabbit Eye irritation – slight irritant	Aroclor 6062. Not Pure Biphenyl Aroclor. Aroclor 6062-Blend of Aroclor 5460 (which is a Terphenyl) and Aroclor 1221

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
80. 1970 (0957) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 6037—MCS 1057-1 Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Oral LD50 (rat) : 4.9 g/kg g/kg/day Skin absorption MLD (rabbit) : >5.0 g/kg and <7.9 g/kg Rabbit Skin irritation –mild irritating Rabbit Eye irritation – slight irritant inhalation: non-toxic	Aroclor 6037
81. 1970 (0965) TOXICOLOGICAL INVESTIGATION OF: MCS 1004--AROCLOR 4273, LOT NUMBER: OR 151723-3 Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Oral LD50 (rat) : 8.9 g/kg Skin absorption MLD (rabbit) : > 2.0 g/kg and <3.2 g/kg Rabbit Skin irritation –non-irritating Rabbit Eye irritation – slight irritant Inhalation – non-toxic	Aroclor 4273. Not Pure Biphenyl Aroclor. Aroclor 4273-40% Terphenyl and 60% Aroclor 73% chlorine
82. 1970 (0974) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 6040—CHLORINATED POLYPHENYL Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Oral LD50 (rat) : 3.3 g/kg Skin absorption MLD 9rabbit) : > 3.2 g/kg and <5.0 g/kg Rabbit Skin irritation –moderate to severe irritation Rabbit Eye irritation – slight irritant Inhalation – non-toxic	Aroclor 6040. Not Pure Biphenyl Aroclor. Blend of Terphenyl and Aroclor.
83. 1970 (0982) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 6070—CHLORINATED POLYPHENYL Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Oral LD50 (rat) : 4.0 g/kg Skin absorption MLD (rabbit) : >7.9 g/kg Rabbit Skin irritation –non-irritating Rabbit Eye irritation – slight irritant Inhalation – non-toxic	Aroclor 6070. Not Pure Biphenyl Aroclor. Blend of Terphenyl and Aroclor.
84. 1970 (0990) TOXICOLOGICAL INVESTIGATION OF: AROCLOR 6090—CHLORINATED POLYPHENYL Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Range finding acute oral toxicity (rat) : >10 g/kg and <12.6 g/kg Skin absorption MLD (rabbit) : >7.9 g/kg Rabbit Skin irritation –non-irritating Rabbit Eye irritation – slight irritant	Aroclor 6090. Not Pure Biphenyl Aroclor. Blend of Terphenyl and Aroclor.
85. No Date-1970?? (0996) **TOXICOLOGICAL STUDIES WITH POLYCHLORINATED BIPHENYLS.** **M.L. Keplinger et al. Industrial Bio-Test Laboratories, Inc.**	**Study prompted by reports of PCBs detected in wildlife. Key findings was evidence of reproductive toxicity and tumor formation.** **1. This is the first Monsanto study that investigates the toxicological effects of CHRONIC exposures.**	**Aroclors 1242, 1254, and 1260. No raw data presented to evaluate.** **Preliminary 30-day rat study conducted to determine the "no apparent effect" of 1254 and 1260.**

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
	Notes that up until this time (1970?) no information on chronic exposures was available. It is also the first study where ingestion from the diet was evaluated. **"Although some toxicological data were available, they were rather limited. Information on chronic effects especially of the PCB's were not available."** **2. First noted appearance of tumors in chickens.**	**2-year rat study used 1, 10 and 100 ppm. 2-year dog feeding study.** **100 ppm 1254 and 1260 caused increased liver weight.** **Three generation study: First generation showed 1254 had reproductive toxicity-lactation index decrease. Mating indices were reduced.** **Second generation showed decreased survival with 1242 and lactation decrease with 1254.** **Chicken fed diet with 1242 and 1254 lower body weight. Chickens also showed "extensive growths" on the kidneys, gonads, liver or heart.**
86. 1971 (1002) REPORT TO MONSANTO COMPANY ACUTE VAPOR INHALATION TOXICITY STUDY WITH MCS 1016 IN ALBINO RATS Donn Hathaway, Industrial BIO-TEST Laboratories, Inc.	Acute inhalation study with 10 rats to a 4-hour period-14-day observation. Endpoint was death from acute exposures. No deaths.	MCS 1016. Aroclor 1016 is a refined Aroclor 1242 developed after 1971.
87. 1971 (1008) REPORT TO MONSANTO COMPANY ACUTE TOXICITY STUDIES WITH AROCLOR 1221, AROCLOR 5442, AND MCS 1016 Carmen Mastri, Industrial BIO-TEST Laboratories, Inc.	Acute study with one dose. Aroclor 1221: Acute oral toxicity, LD50 (rat) : 2.0 g/kg. Acute dermal toxicity, LD50 (rabbit) : 5.0 g/kg Eye irritation-rabbits- minimally irritating. Skin irritation-rabbits- moderately irritating. Aroclor 5442: Acute oral toxicity, LD50 (rat) : 8.4 g/kg. Acute dermal toxicity, LD50 (rabbit) : >10.2 g/kg Eye irritation-rabbits- non-irritating. Skin irritation-rabbits- moderately irritating MCS 1016: Acute oral toxicity, LD50 (rat) : 6.8 g/kg. Acute dermal toxicity, LD50 (rabbit) : 6.0 g/kg Eye irritation-rabbits- non irritating. Skin irritation-rabbits- moderately irritating	Aroclor 1221, 5442, and MCS 1016. Aroclor 5442 is not a pure biphenyl. It is a terphenyl and biphenyl mixture. MCS 1016 is a refined Aroclor 1242 developed after 1971.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
88. 1971 (1049) REPORT TO MONSANTO COMPANY TOXICITY, REPRODUCTION AND RESIDUE STUDY WITH AROCLOR 1242, LOT #AK-255 IN WHITE LEGHORN CHICKENS Dale Flecher, Industrial BIO-TEST Laboratories, Inc.	Subchronic chicken feeding study. Aroclor 2, 4, and 8 ppm mixed in diet for 39 weeks (ave. chicken life span 15 years) No specific effects noted. Tissues were collected and shipped to Monsanto, and Monsanto findings were not reported in this study.	Aroclor 1242. Effect of Aroclor on egg laying.
89. 1971 (1085) TOXICOLOGICAL INVESTIGATION OF: DECACHLOROBIPHENYL–AROCLOR 1272—LOT: OR 179021 Melvin Birch, Younger Laboratories, Inc.	Acute single dose exposure study causing death. Acute Oral MLD (rat) : >7.9 g/kg Skin absorption MLD (rabbit) : >7.9 g/kg Rabbit Skin irritation –non-irritating Rabbit Eye irritation – slight irritant	Aroclor 1272. Blend of Terphenyl and Aroclor.
90. 1971 (1091) REPORT TO MONSANTO COMPANY TERATOGENIC STUDY WITH AROCLOR 1254 IN ALBINO RATS James Plank, Industrial BIO-TEST Laboratories, Inc.	First study to evaluate the teratologic effects of Aroclors on rats. Pregnant rats dosed at 6–15 days of gestation with 10 or 30 mg/kg Aroclor 1242 killed on day 20. Maternal body weight reduction. Percent of females with resorption sites was elevated. Only gross teratogenic observations were made. 12% of fetuses from females administered 30 mg/kg had caudal renal ectopia (abnormal positioning/development of kidney	Aroclor 1254. Fetal death and physical malformations in live fetuses evaluated.
91. 1971 (1111) REPORT TO MONSANTO COMPANY TERATOGENIC STUDY WITH AROCLOR 1242 IN ALBINO RATS James Plank, Industrial BIO-TEST Laboratories, Inc.	Evaluation of the teratologic effects of Aroclors on rats. Pregnant rats dosed at 6–15 days of gestation with 10 or 30 mg/kg Aroclor 1242 killed on day 20. Percent of females with resorption sites was elevated.	Aroclor 1242. Effect of Aroclor on egg laying.
92. 1971 (1129) REPORT TO MONSANTO COMPANY TERATOGENIC STUDY WITH AROCLOR 1260 IN ALBINO RATS James Plank, Industrial BIO-TEST Laboratories, Inc.	Evaluation of the teratologic effects of Aroclors on rats. Pregnant rats dosed at 6–15 days of gestation with 10 or 30 mg/kg Aroclor 1260 killed on day 20. Decrease in pregnant female body weight in both dose groups. Percent of females with resorption sites was elevated.	Aroclor 1260.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
93. 1971 (1147) REPORT TO MONSANTO COMPANY THREE-GENERATION REPRODUCTION STUDY WITH AROCLOR 1242 IN ALBINO RATS Sandra Haley, Industrial BIO-TEST Laboratories, Inc.	Evaluation of the 2nd litter obtained from the 3rd parental generation- reproductive toxicity in rats. Rats were dosed at 1, 10 and 100 ppm The F1 rats had increased brain and liver weights in 100 ppm group. 100 ppm F2 rats had lower mating indices and reduced pregnancies. It was so low, the study was stopped at the F2 stage.	Aroclor 1242.
94. 1971 (1198) REPORT TO MONSANTO COMPANY TWO-YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1254 IN BEAGLE DOGS Bruce Burtner, Industrial BIO-TEST Laboratories, Inc. Paul Wright and M.L.	It states it is a "chronic 2-year toxicity study." It is not a cancer lifetime study. Beagle lifespan is ~13 years in dogs. Dogs were fed PCBs in diet at 1, 10 and 100 ppm. This study found no systemic toxicity or cancer. These findings do not appear to be credible.	Aroclor 1254.
95. 1971 (1276) REPORT TO MONSANTO COMPANY TWO-YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1242 IN BEAGLE DOGS Bruce Burtner, Industrial BIO-TEST Laboratories, Inc. Paul Wright and M.L. Keplinger	It states it is a "chronic 2-year toxicity study." It is not a cancer lifetime study. Beagle lifespan is ~13 years in dogs. Toxicological Parameters Evaluated in 1, 10 and 100 ppm-dosed dogs: Body weight Food Consumption Behavioral Reactions Hematologic Studies Blood Chemistry Studies Urine Analysis This study found no systemic toxicity or cancer. These findings do not appear to be credible.	Aroclor 1242.
96. 1971 (1351) REPORT TO MONSANTO COMPANY TWO-YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1260 IN BEAGLE DOGS Bruce Burtner, Industrial BIO-TEST Laboratories, Inc. Paul Wright and M.L. Keplinger	It states it is a "chronic 2-year toxicity study." It is not a cancer lifetime study. Beagle lifespan is ~13 years in dogs. Toxicological Parameters Evaluated in 1, 10 and 100 ppm-dosed dogs: Body weight Food Consumption Behavioral Reactions Hematologic Studies Blood Chemistry Studies Urine Analysis This study found no systemic toxicity or cancer. These findings do not appear to be credible.	Aroclor 1260.

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
97. 1971 (1426) REPORT TO MONSANTO COMPANY THREE-GENERATION STUDY WITH AROCLOR 1254 IN ALBINO RATS Sandra Haley, Industrial BIO-TEST Laboratories, Inc. James Plank, Paul Wright and M.L. Keplinger	Reproduction study to ascertain potential toxicological effects of subacute oral administration of Aroclor 1254. This report presents data from initiation of the investigation to weaning of the 2nd litters obtained from the 3rd parental generation. Rats fed 1, 10, or 100 ppm Aroclor 1254. Results. Body weight, mortality, reactions, gross pathologic findings, population data: no difference between control and test animals; liver weights and liver to body weight or brain weight ratios were significantly elevated in 100 ppm males; 2nd generation 100 ppm rats had lowered mating indices and reduced incidence of pregnancy; pup survival lower in litters from 100 ppm dams.	Aroclor 1254.
98. 1971 (1477) REPORT TO MONSANTO COMPANY THREE-GENERATION STUDY WITH AROCLOR 1260 IN ALBINO RATS. Sandra Haley, Industrial BIO-TEST Laboratories, Inc. James Plank, Paul Wright and M.L. Keplinger	Reproduction study, subacute oral administration of Aroclor 1260 in 3 generations of rats. Initiation to weaning of 2nd litters from 3rd parental generation. Rats fed 1, 10, or 100 ppm. Results. Body weight, mortality and reactions, gross pathology, lesions, population data, survival, body weights of progeny, pathology of progeny: no differences. Absolute liver weights and liver to body weight or brain weight rations elevated in F0 and F1 males fed 100 ppm.	Aroclor 1260.
99. 1971 (1525) MONSANTO TWO-YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1260 IN ALBINO RATS. Philip Smith, Industrial BIO-TEST Laboratories, Inc. James Plank, Paul Wright and M.L. Keplinger	Chronic oral toxicity study. Rats fed 1, 10, or 100 ppm. Results. Food consumption, body weight gains, mortality, hematological and clinical blood chemistry, urine analyses, organ weights: no change. Liver weights and liver to body weight or brain weight ratios significantly elevated in 100 ppm rats, along with vacuolar changes; focal hypertrophy and focal hyperplasia found in livers of rats fed Aroclor 1260.	Aroclor 1260
100. 1971 (1612) MONSANTO TWO-YEAR CHRONIC ORAL TOXICITY WITH AROCLOR 1254 IN ALBINO RATS. Philip Smith, Industrial BIO-TEST Laboratories, Inc. James Plank, Paul Wright and M.L. Keplinger	2-year chronic toxicity study. Rats fed 1, 10, or 100 ppm Aroclor 1254. Results. Body weight of females at 3 and 12 months, body weight of males at all time points, mortality, hematological and clinical blood chemistry, urine analyses, organ weighs except liver: no change. Body weight at 24 mo. was less in 100 ppm females. Absolute liver weight and liver to body weight or brain weight ratios were significantly elevated in 100 ppm rats, with histologic exam revealing vacuolar changes. Focal hypertrophy and focal hyperplasia in livers of animals fed Aroclor 1254.	Aroclor 1254

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
101. 1971 (1702) MONSANTO TWO-YEAR CHRONIC ORAL TOXICITY WITH AROCLOR 1242 IN ALBINO RATS. Philip Smith, Industrial BIO-TEST Laboratories, Inc. James Plank, Paul Wright and M.L. Keplinger	2-year chronic oral toxicity study. Rats fed 1, 10, or 100 ppm Aroclor 1242. Results. Food consumption, body weight gains, mortality, hematological and clinical blood chemistry studies, urine analyses: no change. Liver weights and liver to body weight or brain weight ratios were significantly elevated in 100 ppm females. 100 ppm livers: vacuolar changes. Focal hypertrophy and focal hyperplasia in livers of rats fed Aroclor 1242.	Aroclor 1242
102. 1971 (1790) ACUTE TOXICITY OF AROCLOR 1016, AROCLOR 1242, AND DDT TO BLUEGIL (LEPOMIS MACROCHIRUS) AND CHANNEL CATFISH (ICTALURUS PUNCTATUS) DURING 21 DAYS CONTINUOUS EXPOSURE TO THE CHEMICALS IN WATER. Bevier Hasbrouck Sleight III, Bionomics, Inc.	Bioassay report. Median tolerance limit (TL50) developed. Results: Test fish behaved similar to chemically poisoned fish at Aroclor concentrations as low as 40 ug/l. Aroclor 1016, bluegill: 7-day TL50=>500.0 ug/l; 14-day TL50=186 ug/l; 21-day TL50=136 ug/l. Aroclor 1016, channel catfish: 7-d TL50=>500.0 ug/l; 14-d TL50=298 ug/l; 21-d TL50-138 ug/l. Aroclor 1242, bluegill: 7-d TL50=339 ug/l; 14-d TL50=163 ug/l; 21-d TL50=71.9 ug/l. Aroclor 1242, channel catfish: 7-d TL50=500.0 ug/l; 14-d TL50=391 ug/l; 21-d TL50=289 ug/l. DDT, bluegill: 7-d TL50=1.39 ug/l; 14-d TL50=0.887 ug/l; 21-d TL50=0.823 ug/l. DDT, channel catfish: 7-d TL50=>5.0 ug/l; 14-d TL50=3.83 ug/l; 21-d TL50=2.61 ug/l.	Aroclor 1016, Aroclor 1242, and DDT. Toxicity analyzed in bluegill and channel catfish over 21 days of continuous exposure to the chemicals in the water.
103. 1971 (1799) REPORT TO MONSANTO COMPANY. NINETY-DAY SUBACUTE ORAL TOXICITY STUDY WITH AROCLOR 1221 IN BEAGLE DOGS. Bruce Burtner, Industrial BIO-TEST Laboratories, Inc. Paul Wright and M.L. Keplinger	90-day subacute oral toxicity study. Dogs fed 1, 10, and 100 ppm for first 28 days. After 28 days, lowest level was increased from 1 ppm to 300 ppm; other levels remained the same. Results. No significant abnormalities	Aroclor 1221. Body weight, food consumption, behavioral reactions, mortality, hematologic studies, blood chemistry studies, urine analyses, gross pathologic studies, histopathologic studies.
104. 1971 (1854) Manuscript for Toxicol. Appl. Pharmacol. TOXICOLOGICAL STUDIES OF THREE POLYCHLORINATED BIPHENYLS. O. Fancher, M.L. Keplinger, E.P. Wheeler, and J.C. Clandra. M.L. Keplinger co-author	Background review	Aroclor 1242, Aroclor 1254, Aroclor 1260
105. No date (1869) RESULTS OF FOUR-DAY STATIC FISH TOXICITY STUDIES RAINBOW TROUT. Industrial BIO-TEST Laboratories, Inc.	1.0% and 10.0% (w/v) soln in acetone. 4-day TL50: >1.0 ppm	Aroclor 1260

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
106. No date (1871) RESULTS OF FOUR-DAY STATIC FISH TOXICITY STUDIES RAINBOW TROUT AND BLUEGILLS. Gary Rausina, Industrial BIO-TEST Laboratories, Inc.	1.0% and 10.0% (w/v) solution in acetone 4-day TL50 (rainbow trout) : >10 ppm and <100.0 ppm; 4-day TL50 (bluegill) : >10 ppm and <100.0 ppm	Aroclor 1242
107. 1972 (1873) FOUR-DAY STATIC FISH TOXICITY STUDIES WITH AROCLOR 1221, AROCLOR 5432, AROCLOR 5442, AROCLOR 5460, AND MCS 1016 IN BLUEGILLS AND CHANNEL CATFISH John Hamlin, Industrial BIO-TEST Laboratories, Inc.	3 types of assay: 1) test material and fish exposure; 2) blank exposure (without fish) ; 3) control exposure (without test material) . Aroclor 1221 (bluegill) : TL50=0.23 ppm. Aroclor 1221 (channel catfish) : TL50=3.34 ppm. Aroclor 5432 (bluegill) : TL50= >100.0 ppm. Aroclor 5432 (channel catfish) : TL50=>100.0 ppm. Aroclor 5442 (bluegill) : TL50= >100.0 ppm. Aroclor 5442 (channel catfish) : TL50=>100.0 ppm. Aroclor 5460 (bluegill) : TL50= >100.0 ppm. Aroclor 5460 (channel catfish) : TL50=>100.0 ppm. MCS 1016 (bluegill) : TL50=0.65 ppm. MCS 1016 (channel catfish) : TL50-0.75 ppm	Aroclor 1221, Aroclor 5432, Aroclor 5442, Aroclor 5460, MCS 1016. Determining TL50
108. 1972 (1902) TOXICOLOGICAL INVESTIGATION OF: MCS 1230 GERMAN MINE FLUID—Lot: OR 162483. Melvin Birch, Younger Laboratories, Inc.	Acute oral and skin absorption minimal lethal dose, as well as skin irritation, eye irritation, vapor inhalation. Acute oral MLD (rat) : >10 g/kg and <12.6 g/kg. Acute skin absorption MLD (rabbit) : >7.9 g/kg. Skin irritation (rabbit) : non-irritating. Eye irritation (rabbit) : slight irritant. Vapor inhalation, ambient temp (rat) : nontoxic. Vapor inhalation, 150°C (rat) : nontoxic.	MCS 1230
109. 1972 (1911) MUTAGENIC STUDY WITH AROCLOR 1260 IN ALBINO MICE. Dennis Arnold, Industrial BIO-TEST Laboratories, Inc. M.L. Keplinger reviewed study.	Dominant lethal mutagenic study. Single IP injection at 0.5 mg/kg or 1.0 mg/kg. Mating indices, implantation site, resorption sites, embryos, and mutation rates were unchanged.	Aroclor 1260
110. 1972 (1928) MUTAGENIC STUDY WITH AROCLOR 1254 IN ALBINO MICE. Dennis Arnold, Industrial BIO-TEST Laboratories, Inc. M.L. Keplinger reviewed study.	Dominant lethal mutagenic study. Single IP injection at 0.5 mg/kg or 1.0 mg/kg. Mortality: 3 rats treated with 1 g/kg died within 2 days, and 2 control rats died over course of study. Mating index: somewhat low for 1.0 mg/kg at 4 and 6 weeks. Autopsy and mutation: no changes.	Aroclor 1254
111. 1972 (1944) MUTAGENIC STUDY WITH AROCLOR 1242 IN ALBINO MICE.	Dominant lethal mutagenic study. Single IP injection at 0.5 mg/kg or 1.0 mg/kg.	Aroclor 1242

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
Dennis Arnold, Industrial BIO-TEST Laboratories, Inc. M.L. Keplinger reviewed study.	No change in ability of males to mate with or fertilize untreated males, mutation indices, or dominant lethality.	
112. 1972 (1962) 90-DAY SUBACUTE ORAL TOXICITY STUDY WITH MCS 1016 IN BEAGLE DOGS. Bruce Burtner, Industrial BIO-TEST Laboratories, Inc. M.L. Keplinger reviewed study.	90-day subacute oral toxicity at 1) 1 ppm (days 1–28) to 30 ppm (days 29–90) ; 2) 10 ppm (days 1–28) to 300 ppm (days 29–90) ; and 3) 100 ppm. Results: No changes in body weight, food consumption, behavioral reactions, mortality, hematologic studies, blood chemistry studies, urine analyses, gross pathologic studies, or histopathologic studies.	MCS 1016. Measured body weight, food consumption, behavioral reactions, mortality, hematologic studies, blood chemistry studies, urine analyses, gross pathologic studies, and histopathologic studies.
113. 1972 (2017) 90-DAY SUBACUTE ORAL TOXICITY STUDY WITH MCS 1016 IN ALBINO RATS. Philip Smith, Industrial BIO-TEST Laboratories, Inc. Paul Wright, James Plank and M.L. Keplinger reviewed study.	90 days feeding of rats at 30 ppm, 100 ppm, and 300 ppm. Results: significant elevation in liver weights and ratios for female rats feed 300 ppm. No other changes in body weight, food consumption, survival, hematologic studies, clinical blood chemistry, urologic studies, or gross and microscopic pathologic studies.	MCS 1016. Measured body weight, food consumption, survival, hematologic studies, clinical blood chemistry, urologic studies, and gross and microscopic pathologic studies.
114. 1972 (2049) 90-DAY SUBACUTE ORAL TOXICITY STUDY WITH AROCLOR 1221 IN ALBINO RATS. Philip Smith, Industrial BIO-TEST Laboratories, Inc. Paul Wright, James Plank and M.L. Keplinger reviewed study.	90-day feeding of rats at 10, 100, and 300 ppm. Results: no changes in body weight gain, food consumption, survival, hematologic studies, clinical blood chemistry, urologic studies, gross and microscopic pathologic studies, or organ weights or ratios.	Aroclor 1221.
115. 1972 (2081) TOXICITY, REPRODUCTION AND RESIDUE STUDY WITH MCS 1016 IN WHITE LEGHORN CHICKENS. Dale Fletcher, Industrial BIO-TEST Laboratories, Inc. M.L. Keplinger reviewed study.	Toxicity, reproduction, and residue study. Chickens fed 1, 3, or 10 ppm compound. Results. Mortality: 6 females deaths: 1 control, 2 in 1 ppm group, 1 in 3 ppm group, and 2 in 10 ppm group. No abnormalities or systemic signs of toxicity attributable to MCS 1016. Egg production and quality was normal. Hatchability in 3 ppm group was lower than control, 1 ppm, and 10 ppm groups. No differences in specific gravity and shell thickness of eggs. No differences in body weight, viability of chicks, or gross pathologic changes in chicks.	MCS 1016
116. 1972 (2109) TOXICITY, REPRODUCTION AND RESIDUE STUDY WITH AROCLOR 1221 IN WHITE LEGHORN CHICKENS. Dale Fletcher, Industrial BIO-TEST Laboratories, Inc.	Toxicity, reproduction, and residue study in chickens. Doses of 1 ppm, 3 ppm, and 10 ppm. Results. Body weights, food consumption, gross pathology, and systemic signs of toxicity are normal. Egg production was lower for control birds, and percentage of defective eggs was greater in the control group. No differences in specific gravity and shell thickness. Hatchability	Aroclor 1221

Year, Study Title, and Authors	Study Type/Importance of Study/Key Finding	Type of Aroclors/PCBs Analyzed/Health Effect Investigated
M.L. Keplinger	of eggs was slightly lower in the 10 ppm than for the other groups.	
117. 1972 (2137) FOUR-DAY FISH TOXICITY STUDIES WITH AROCLOR 1242, AROCLOR 1254, AND AROCLOR 1260 IN BLUEGILLS AND CHANNEL CATFISH. Kenneth Ebbens, Industrial BIO-TEST Laboratories, Inc. M.L. Keplinger	4-day fish toxicity studies in 3 bioassay conditions: 1) Aroclor and fish; 2) blank (no fish) ; and 3) control (fish but no aroclor) . Results. Aroclor 1242 (bluegill) : TL50=0.24 ppm. Aroclor 1242 (channel catfish) : TL50=0.13 ppm. Aroclor 1254 (bluegill) : TL50= >100.0 ppm. Aroclor 1254 (channel catfish) : TL50=~0.20 ppm. Aroclor 1260 (bluegill) : TL50=>100.0 ppm. Aroclor 1260 (channel catfish) : TL50=>100.0 ppm.	Aroclor 1242, Aroclor 1254, Aroclor 1260.

EXHIBIT H

PCBs in Municipal Products

REVISED



Pg. 12 Revised July 21, 2015

Ecology Municipal Stormwater Grants of Regional or Statewide Significance
Grant No. G1400545

Prepared by:

City of Spokane
Wastewater Management Department

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Contents

PCBs in Municipal Products

INTRODUCTION

Polychlorinated biphenyls (PCBs) are a toxic manmade chemical found ubiquitously in the environment. Historically, PCBs were primarily used in coolants and lubricants in electrical equipment, such as transformers and capacitors. In the United States, PCBs were largely sold under the trade name Aroclor. Direct production of PCBs was halted in the US in the 1970's due to evidence of human toxicity and persistence in the environment. Since that time, however, PCBs have been incidentally produced in a multitude of manufacturing processes as an unintended byproduct of processes that use heat, chlorine, and carbon.

The Washington State 2008 303(d) list holds 113 Category 5 listings for PCBs, covering 59 waterbodies. Several segments of the Spokane River are included in this list. The City of Spokane has performed stormwater sampling in several of its outfalls that drain to the Spokane River. PCBs were detected in each sample, with a typical sample in the range of 7,000 picograms per liter (pg/L), or parts per quadrillion (ppq).

Once thought to be only a legacy contaminant, PCBs have been found in numerous commercially available products. These PCBs are not intentionally produced, but are rather unintended byproducts of the manufacturing process. Materials containing less than 50 parts per million (ppm) are not considered "PCB-contaminated" under the Toxics Substances Control Act (TSCA) (40 CFR 761.3). For comparison to water quality considerations, 50 ppm is equivalent to 50,000,000,000 ppq. The current Washington State human health surface water quality standard for PCBs is 170 ppq (derived from the National Toxics Rule, 40 CFR 131.36). The Spokane Tribe adopted a water quality standard of 1.3 ppq due to higher fish consumption rates used to derive the standard.

Many products can easily come into contact with rain water and contribute to PCB concentrations in stormwater runoff. Municipalities are concerned about the presence of PCBs in commonly used products such as road paint, asphalt sealers, pesticides, and de-icer, to name a few. However, limited data is available as to the concentration of PCBs in products used for road and facility maintenance.

Nearly 50 product samples were collected and analyzed for PCBs using EPA Method 1668C. This method is capable of detecting low concentrations of PCBs for all 209 congeners. The majority of samples were composed of roadway, pipe, and vehicle maintenance products. Because PCBs are also ubiquitously detected in sanitary wastewater samples, five personal care products were sampled as well.

PCB 101

Chemical Structure

PCB molecules are composed of two joined benzene rings with varying degrees of chlorination, as depicted in Figure 1. PCBs can have between one and ten chlorine atoms. There are 209 different arrangements of this molecule, each known as a congener. Congeners are named PCB-1 through PCB-209, with greater numbers corresponding to greater degrees of chlorination. Homologues are the group of PCB molecules having the same degree of chlorination. For example, monochlorobiphenyls (monoCB) is the group of PCBs having one chlorine, dichlorobiphenyls (diCB) are the group of PCBs having two chlorines, etc.

MonoCBs =	1 chlorine
DiCB =	2 chlorines
TriCB =	3 chlorines
TetraCB =	4 chlorines
PentaCB =	5 chlorines
HexaCB =	6 chlorines
HeptaCB =	7 chlorines
OctaCB =	8 chlorines
NonaCB =	9 chlorines
DecaCB =	10 chlorines (PCB-209)

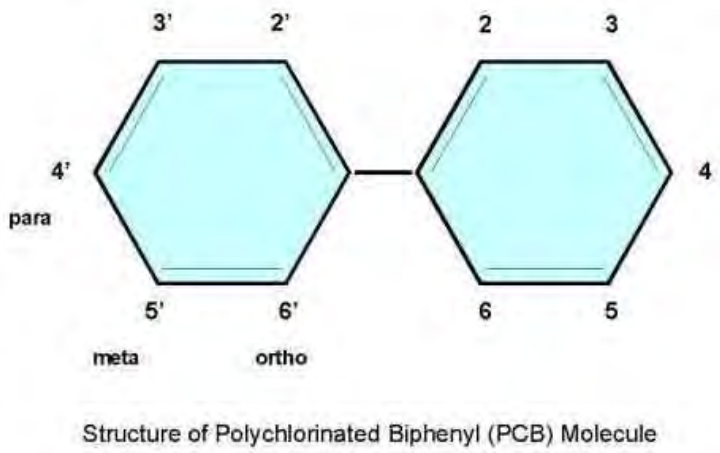

Figure 1. (EPA, 2010b)

During the laboratory analytical process, some congeners cannot be distinguished from one another and are quantified as a complex of more than one congener. These are known as coeluting congeners, and are denoted with a slash in the figures in this report (e.g. 5/8).

Aroclors

Monsanto was the major US manufacturer of PCBs, and sold them under the trade name Aroclor until 1977 (Erickson, 1986). Aroclors were made of standard PCB mixtures to achieve the desired

chemical properties. Each type of Aroclor was given a 4-digit identification number, with the second two digits indicating percentage of chlorine by weight (ASTDR, 2000). For example, Aroclor 1254 contains about 54% chlorine by weight. Homologue patterns for standard Aroclor mixes are shown in Appendix A. Homologue patterns for environmental and product samples can be compared to homologue patterns for Aroclors to give clues as to whether the PCB content may be a legacy Aroclor or not.

METHODOLOGY

Product Selection

Municipalities use numerous products in the roadway environment for construction, traffic safety, and maintenance purposes. Little is known about the PCB content in these products. To help guide product sampling, a literature search was performed to determine the potential for products to contain PCBs. In general, processes that involve chlorine, carbon, and high temperatures have the potential to inadvertently produce PCBs (Munoz, 2007).

Numerous studies have associated pigments with inadvertent PCB production (Christie, 2014; Ecology, 2014; Hu and Hornbuckle, 2010; Rodenburg, 2012). In particular, yellow pigments and white pigments (titanium dioxide) are associated with PCB-11, 206, 208, and 209. Yellow, orange, and red products that are derived from azo pigments (monoazo (Hansa Yellows and azonaphthols) and diarylide yellows) are associated with inadvertent PCB production, as are phthalocyanine blues and greens. Therefore, many items sampled for this study contained colored items. Various yellow and white road paints were sampled as well as hydrant paint and utility locate paint. Personal care products were selected that contain pigments.

Inadvertent PCB production is also associated with the manufacture of a multitude of various other chlorinated chemicals. Table 1 shows chemicals associated with various products that can be exposed to stormwater or enter the wastewater system:

Table 1. Example of Chemicals Associated with Inadvertent PCB Production

Chemical	Associated Products
Ethylenediamine	Surfactants, fungicides, fuel additives, EDTA, hair care products, soaps
Ethylene dichloride	Polyvinyl chloride (PVC), solvents
Phenylchlorosilanes	Silicones: lubricants, adhesives, coatings, hoses
Chlorinated benzidines	Pigments
Chlorinated paraffins	Flame retardants in plastics, paints, adhesives, sealants, and caulks
Glycerol/Glycerin (synthesized by epichlorohydrine)	Toothpaste, numerous personal care products, antifreeze, resins

(Information in this table adapted from Munoz, 2007)

One of the most consistent illicit discharge complaints received by the City of Spokane is vehicles dripping fluids onto the roadway. In 2011, the City sampled various off-the-shelf motor oils and transmission fluid to assess the potential for PCBs to enter stormwater through this pathway. PCBs were detected in appreciable concentrations in each of the samples, as shown in Table 2. Because PCBs are known to be present in these materials, additional motor oils and other petroleum products were sampled for this product sampling study.

Table 2. Oil and Transmission Fluid Sample PCB Concentrations (City of Spokane, 2011)

Sample	Total PCB, micrograms per kilogram (ppb) (EPA Method 1668)
Pennzoil SAE5W-30	37.8
Quaker State SAE5W-30	14
Valvoline Mercon V	49.5
Red Line D4 Automatic Transmission Fluid	8.8
Valvoline Full Synthetic 5W-30	116

One of the objectives of this project is to inform municipalities across the state. To gain a better understanding of which products and brands are most widely used, a survey was distributed across the state to willing participants. Ten jurisdictions responded, 6 from eastern Washington and 4 from western Washington. Results of the survey showed that one traffic paint brand is commonly used on both sides of the state under a state contract with WSDOT. Other product brands varied widely across the region, and the brand names used by the City of Spokane were not uncommon, so the products available at the City of Spokane were sampled.

Quality Assurance Project Plan (QAPP)

A QAPP was prepared for this project and approved by Ecology prior to the collection of samples (LimnoTech, 2014). A copy of the QAPP is available upon request.

Experimental Design

Ultra clean sampling techniques were followed to reduce the chance of sample contamination from ambient sources. Samples were collected August to October, 2014. Products were placed directly into laboratory-prepared sample jars whenever possible. Where equipment was necessary to remove the sample from its container and place it into the sample jar, clean decontaminated equipment was used.

Each product was assigned a three-digit Product ID number. Liquid and gel samples were placed in 40-milliliter glass vials. Solid samples were placed in 4-ounce glass jars. Pipe samples were wrapped in aluminum foil. Spray paint samples were sent to the laboratory in the original spray cans. All readily available product information was recorded at the time of sampling, including product type, brand name, lot number, manufacture date and country of origin in addition to standard sampling information such as time and date, sampler, and sample location.

Four field replicate samples were collected for field sampling quality control purposes. Replicate samples were collected for product ID 001, 003, 008, and 018.

A chain of custody form was filled out for each sample batch. Samples were packed into coolers, chilled to a maximum of four degrees Celsius, and shipped to Pacific Rim Laboratories for analysis. Samples were analyzed using EPA Method 1668C for all 209 PCB congeners.

Laboratory Quality Control

The laboratory maintains internal quality control procedures, including method blanks, laboratory control samples, laboratory duplicates, and labeled compound, cleanup, internal, and injection standards. In addition, data verification was performed by the City's project quality assurance (QA) officer. Data was validated by both the laboratory and the QA officer and was found to be acceptable.

EPA Method 1668 detects PCBs at very low concentrations. PCBs are truly ubiquitous and can be detected in even the most pristine laboratory environment. Therefore, PCBs are frequently detected in blank samples. To account for this, any congener that was detected in a product sample that was within three times the concentration detected in the associated blank sample were removed from the total PCB value. These congeners are also not included in the graphs in this report.

RESULTS AND DISCUSSION

The results of PCB product sampling are summarized in Table B-1 of Appendix B and in more detail in the following sections. PCBs were detected in all but two of the products that were sampled in the parts per trillion to parts per million range. The units reported by the laboratory are in micrograms per kilogram (ug/kg), or parts per billion. Note that Spokane water quality standards are 1.3 picograms per liter, or parts per quadrillion. One part per billion is 1,000,000 times greater than one part per quadrillion. Therefore, products detected at these concentrations are of concern to water quality practitioners.

Traffic Marking Samples

Several traffic paint samples were collected due to the association between yellow and white pigments and PCBs. One brand of traffic paint is predominantly used by municipalities and agencies throughout the state, sold by Ennis-Flint. Various types of this paint brand are available. Product numbers 983711 and 983712, low VOC, 100% acrylic waterborne traffic line paint, were sampled from the end of a spray nozzle in a City of Spokane shop. A liquid sample, replicate liquid sample, and a dried sample were analyzed (each for white and yellow). The paint was collected in a clean glass beaker and then immediately distributed to each of the sample vials. Dried paint samples were created by City of Spokane staff by pouring a small amount of paint onto a clean Teflon liner and allowing it to dry before sending it to the laboratory for analysis. The purpose of analyzing the dried sample was to determine if some PCB congeners are volatilized after paint application. Ennis-Flint PreMark thermoplastic road striping was also sampled, both in yellow and white.

For comparison, a lesser-used brand of road paint was sampled. Sherwin-Williams Promar solvent based acrylic traffic marking paint is used by some municipalities in southeast Washington. Samples were collected for both yellow and white paint. Replicates of all of the traffic marking samples (except the dried paint) were shipped to Ecology for their own product sampling study. Results of Ecology's analysis will be reported by Ecology. Total PCBs are shown in Tables 3 and 4 along with the percentage of the three most prevalent congeners, PCB-11, 77, and 209.

Table 3. Yellow Traffic Marking

Type	Total PCB (ug/kg)	PCB-11	PCB-77	PCB-209
Ennis	0.73	7%	35%	36%
Ennis (replicate)	2.69	17%	58%	8%
Ennis (dried)	0.565	9%	39%	35%
Promar	64.88	98%	1%	0%
Thermoplastic	10.78	79%	1%	0%

Table 4. White Traffic Marking

Type	Total PCB (ug/kg)	PCB-11	PCB-77	PCB-209
Ennis	0.41	18%	0%	61%
Ennis (replicate)	0.4	23%	0%	57%
Ennis (dried)	0.38	17%	0%	69%
Promar	0.28	41%	1%	0%
Thermoplastic	3.33	22%	0%	0%

Figure 2 shows the congener patterns for both the wet and dried Ennis yellow traffic marking paint samples. Generally the same congeners were detected in each of the samples, with slightly lower concentration in the dried sample than the liquid paint sample. This suggests that some congeners may be volatilizing into the air. However, as the difference in the liquid and duplicate liquid sample show, further study would be warranted to better determine volatilization rates. The Material Safety Data Sheet (MSDS) indicates that the paint composition contains methyl alcohol, titanium dioxide, propylene glycol, 2-butyoxyethanol, and quartz. Pigment content is not listed.

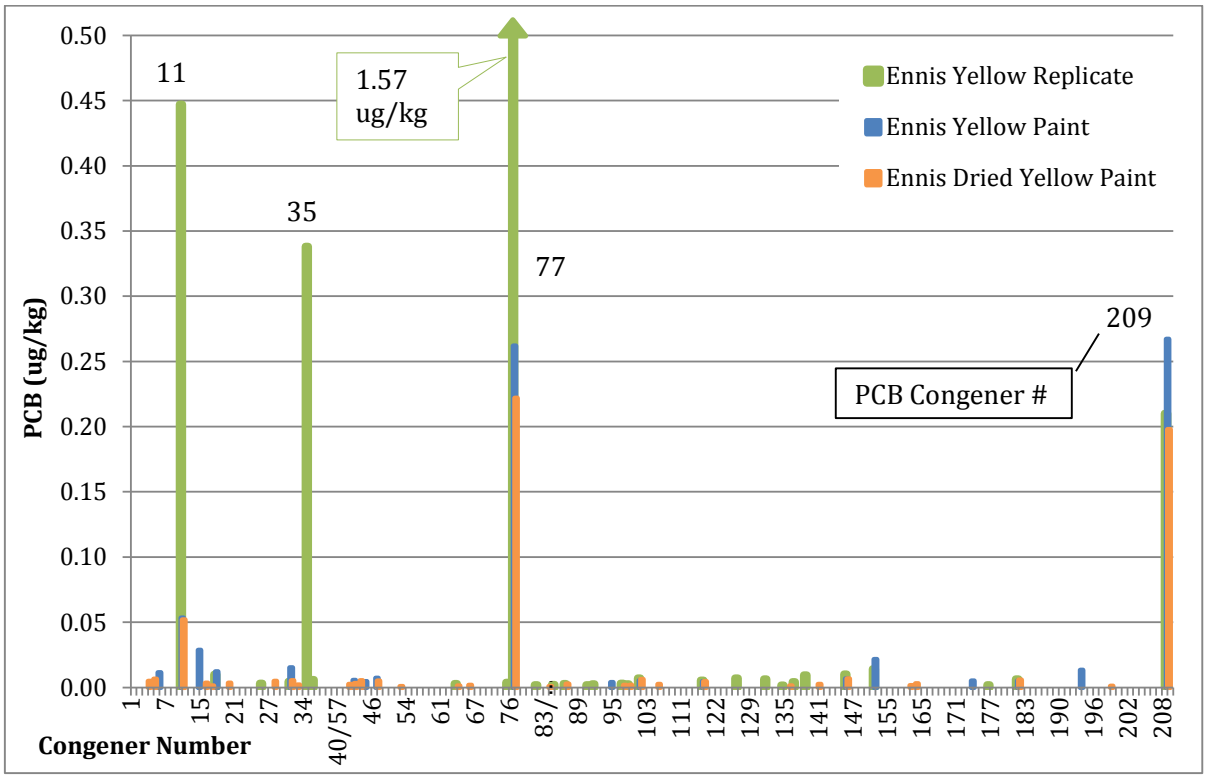

Figure 2. Ennis Wet and Dried Yellow Paint PCB Congeners

Figure 3 shows the congener patterns for the wet and dried Ennis white paint samples. The congener patterns are similar between the three samples. There is no discernible difference between the liquid and dried samples. Interestingly, PCB-11 was detected in the white paint samples in greater concentration than two of the yellow paint samples, although PCB-11 is usually associated with yellow pigment. The concentration of PCB-209 is similar between the yellow and white samples. The MSDS sheets for these products indicate that the yellow paint contains 3-7% titanium dioxide and the white paint contains 7-13% titanium dioxide.

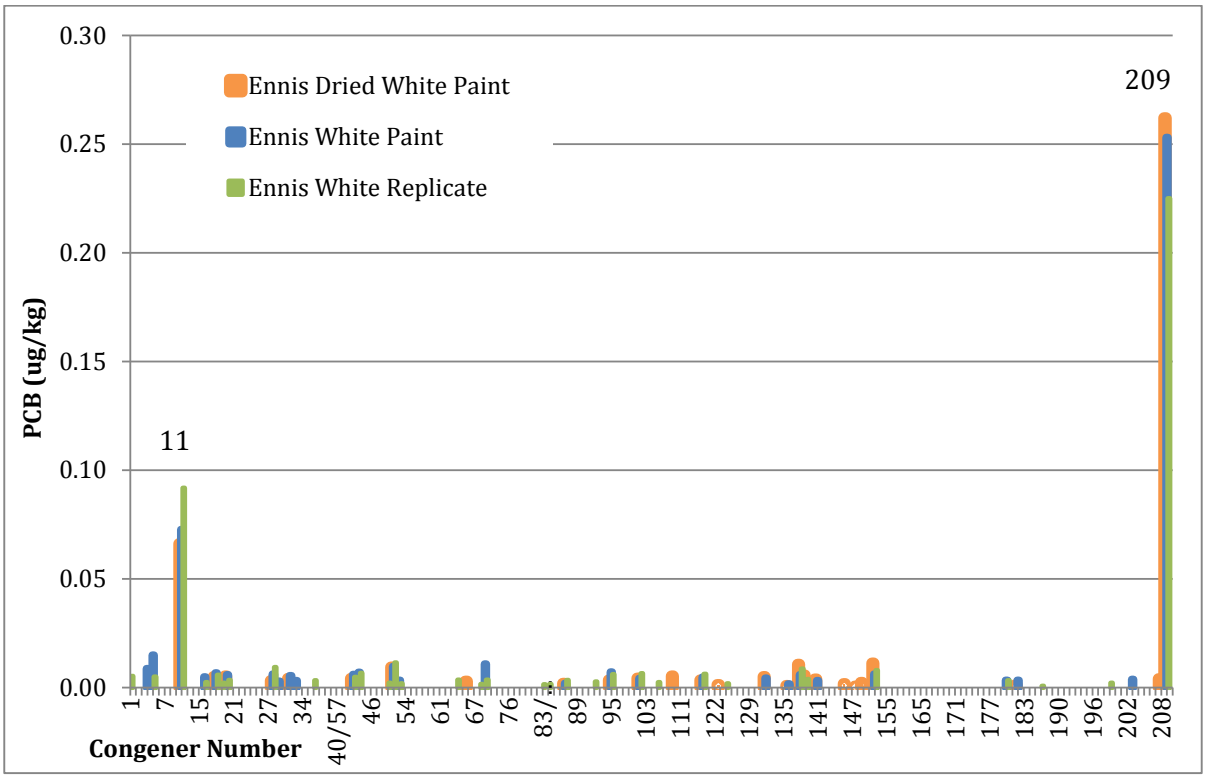

Figure 3. Ennis Wet and Dried W Paint PCB Congeners

Sherwin-Williams Promar yellow and white paint samples are shown in Figure 4. PCB-11 was detected in the yellow paint sample at a significant concentration of 63.8 ug/kg. PCB-35 and 77 were detected similar to the Ennis paint, but PCB-209 was not detected. The MSDS indicates that both white and yellow paints contain ethylbenzene, xylene, acetone, quarts, and titanium dioxide (2% titanium dioxide by weight for yellow and 4% for white). Both yellow and white paints contain approximately 55% pigment by weight.

Figure 5 shows congener patterns for the yellow and white Ennis-Flint PreMark thermoplastic tape samples. Total PCBs are greater than the paint samples (see Table 4 and 5), and there are more congeners detected. Most of the congeners are in the mono-CB through tetra-CB range (having one through four chlorine atoms). The MSDS for this product indicates that it contains the following components in increasing order of concentration: pigments, alkyd resins, polymers, fillers, and glass beads.

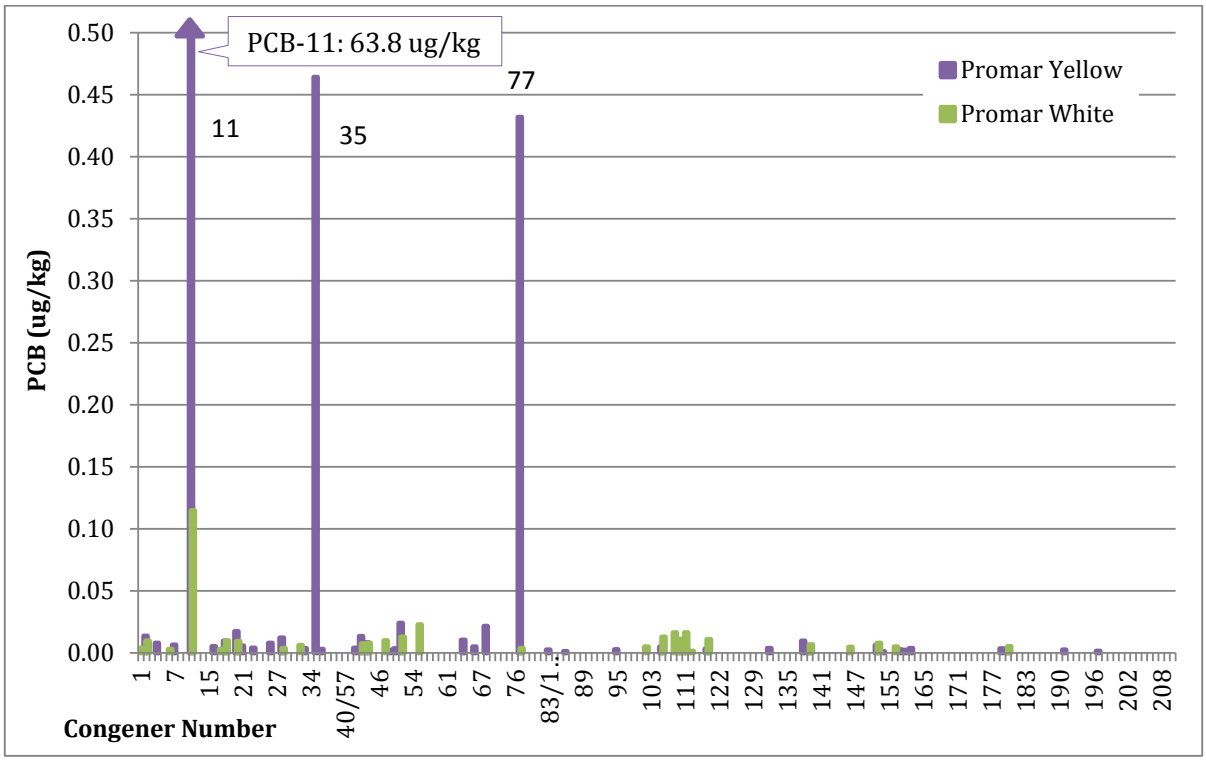

Figure 4. Sherwin-Williams Promar Yellow and White Paint Congeners

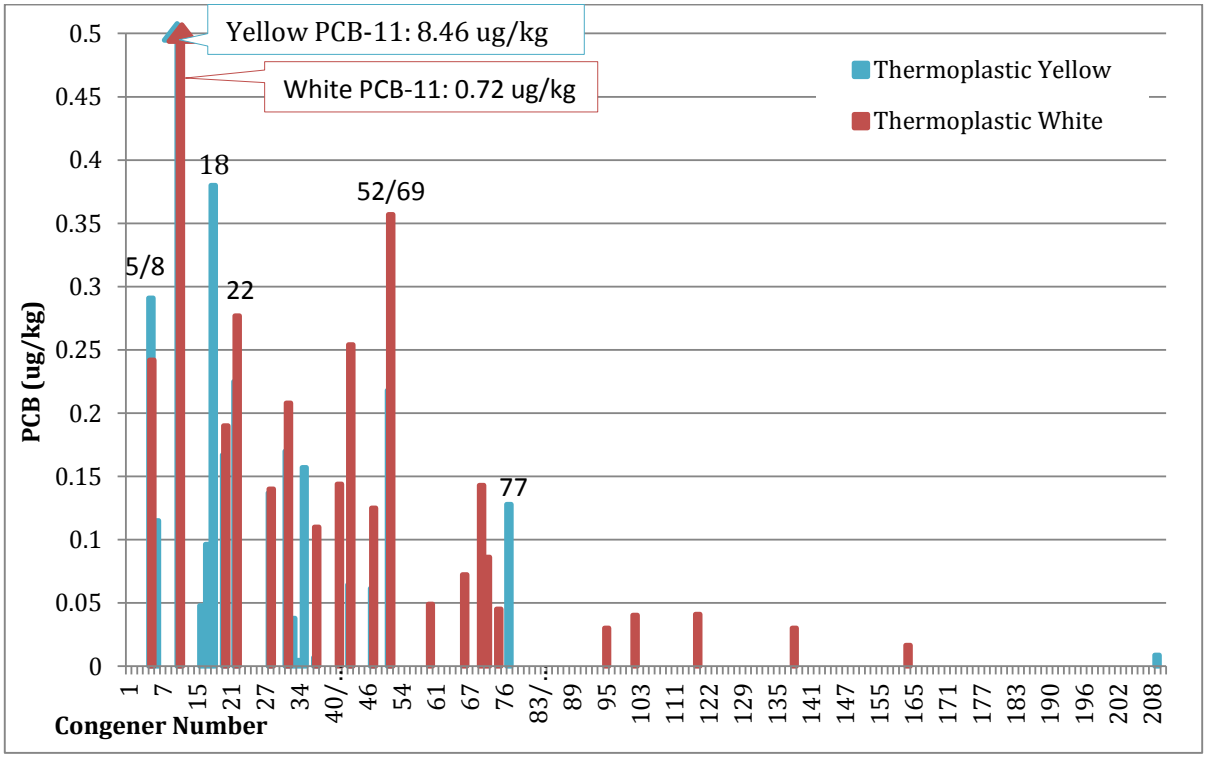

Figure 5. Ennis PreMark Thermoplastic Tape Congners

For samples that have a wide array of PCB congeners, such as the white thermoplastic tape sample, a homologue pattern graph can be a useful tool. These graphs depict the percentage of various homologues that make up the total PCB sample. Figure 6 shows the homologue patterns for both the yellow and white thermoplastic tape samples. The white thermoplastic tape, in particular, has a similar homologue and congener pattern to Aroclor 1016 (Appendix A). Yellow thermoplastic tape also has a similar pattern, but is dominated by PCB-11, a diCB. Aroclor 1016 was one of the lesser used Aroclor mixtures and was used in capacitors.

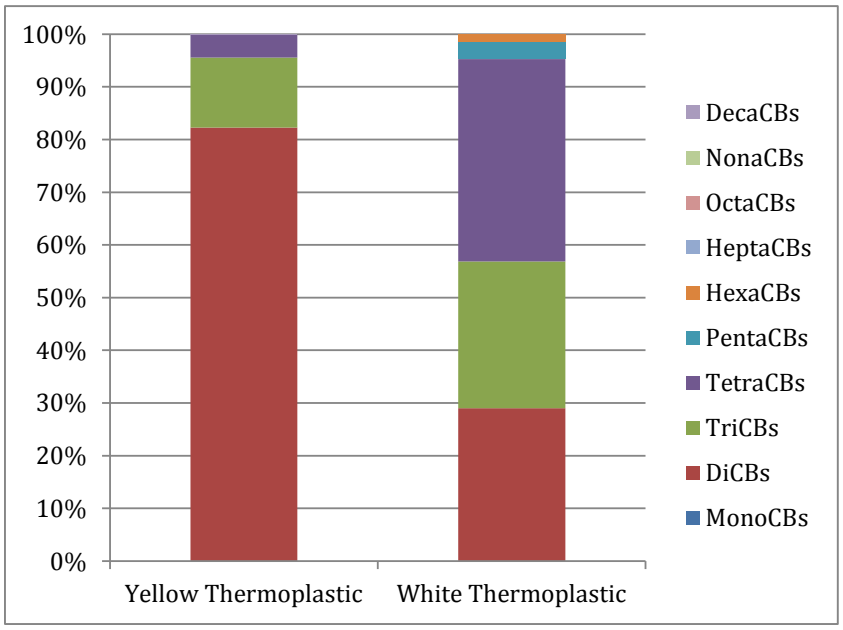

Figure 6. Thermoplastic Tape Homologue Patterns

Hydrant and Utility Locate Paints

Two additional types of paint commonly used on or near roadways were sampled. Fire hydrants are re-painted periodically using spray cans, typically in an aluminum color on the barrel and red on the nozzles. Rustoleum Professional High Performance Enamel Fast-Dry spray paint in Silver Aluminum was sampled. The product contains acetone, liquefied petroleum gas, toluene, xylene, aluminum flake, and ethylbenzene. Total PCBs detected in the sample were **0.0032 ug/kg**, consisting of only the congener PCB-19.

Utility locate paint is sprayed on or near the roadway frequently to mark underground utilities in a variety of colors, including pink, white, green, blue, purple, yellow, orange, and red. The green color denoting sewer utilities was sampled. The product sampled was Rustoleum Industrial Choice Solvent-Based Precision Line inverted marking paint in safety green. The total PCBs detected were **21.527 ug/kg**.

Ingredients listed on the green utility locate paint MSDS include acetone, liquefied petroleum gas, aliphatic hydrocarbon, limestone, xylene, modified alkyd, barium sulfate, talc, naptha (petroleum,

hydrotreated light), titanium dioxide, ethylbenzene, and toluene. Most of the ingredients listed on the MSDS (with the exception of titanium dioxide) are not specifically listed as having the potential to inadvertently produce PCBs in the Munoz (2007) paper, although there may be unlisted intermediate compounds that may produce PCBs. The most likely source of PCB is the pigment, and is most likely a phthalocyanine green based on the presence of PCB-11, 206, 207, 208, and 209. Titanium dioxide may also be contributing to the PCB-206, 208, and 209. On the Rustoleum product website, "phthalo green" is a common pigment used in various paint products, although not specifically listed for this product. The pigments used are proprietary information and would not be shared by the company.

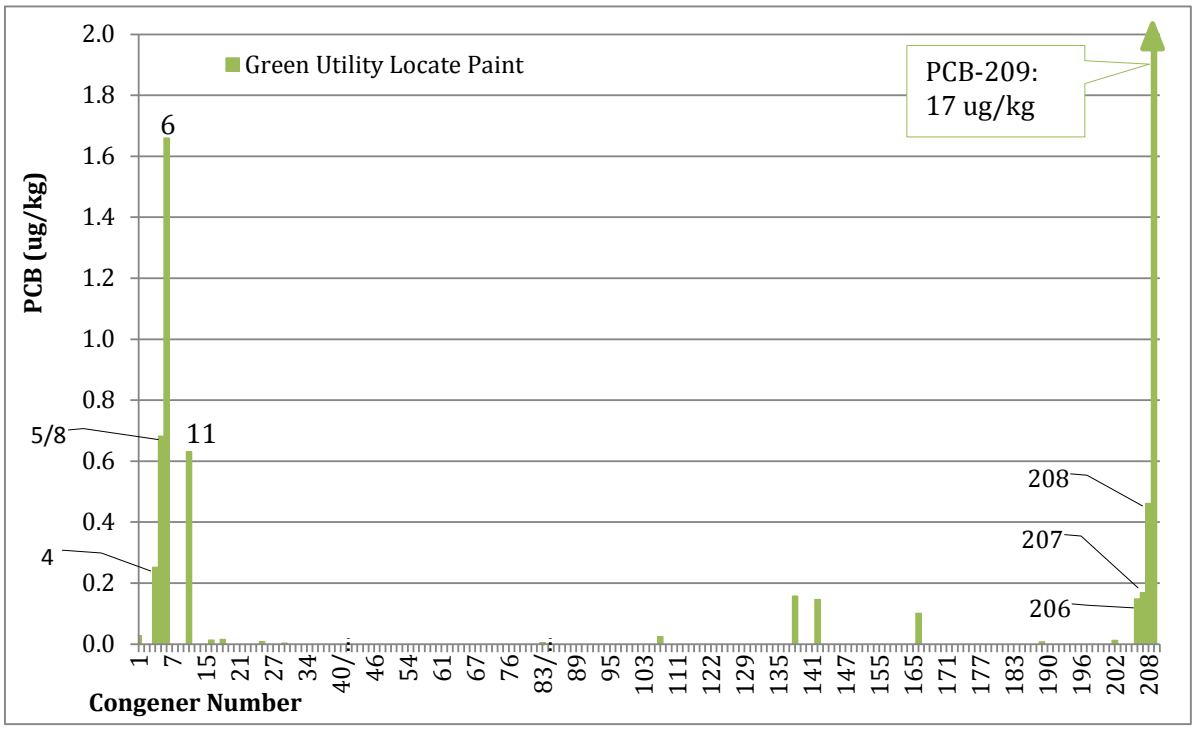

Figure 7. Green Utility Locate Paint Congeners

Deicer

The City of Spokane uses FreezeGard magnesium chloride for roadway deicing. Of the municipalities surveyed, most in eastern Washington use magnesium chloride while most in western Washington use calcium chloride. The Washington State Department of Transportation (WSDOT) Eastern Region uses an enhanced salt brine with sugar beet boost. Both the City of Spokane and WSDOT deicers were sampled. Total PCBs are shown in Table 5.

Table 5. Deicer Total PCB

Sample	Total PCB (ug/kg)
Magnesium Chloride	1.332
Magnesium Chloride Replicate	1.952
SB Boost	0.038

The magnesium chloride is sourced from naturally occurring minerals in the Great Salt Lake.

The magnesium chloride samples were dominated by tetraCBs, while the SB Boost sample congeners were distributed between the triCB to heptaCB range. Homologue patterns are shown in Figure 8 and congener patterns are shown in Figure 9.

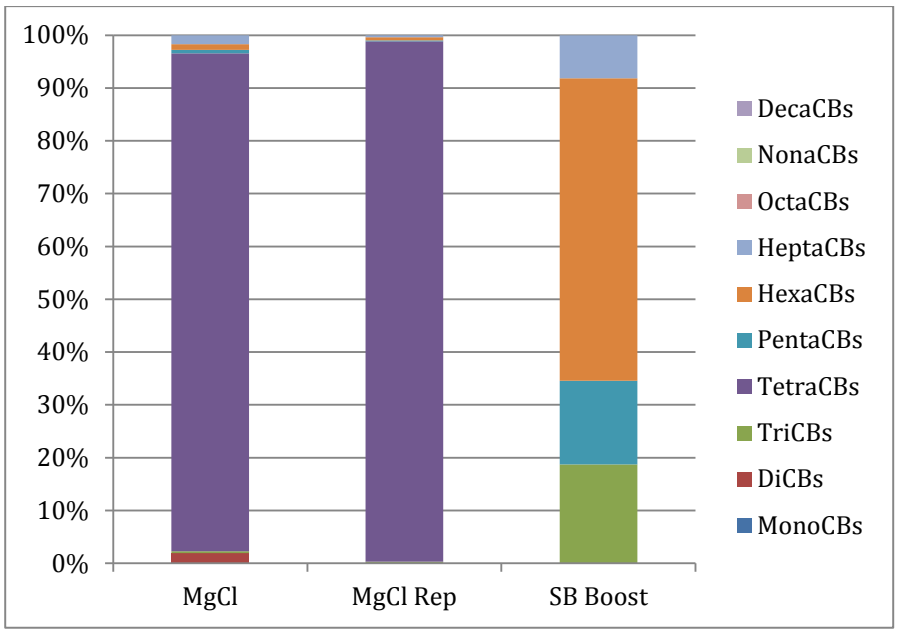

Figure 8. Deicer Homologue Patterns

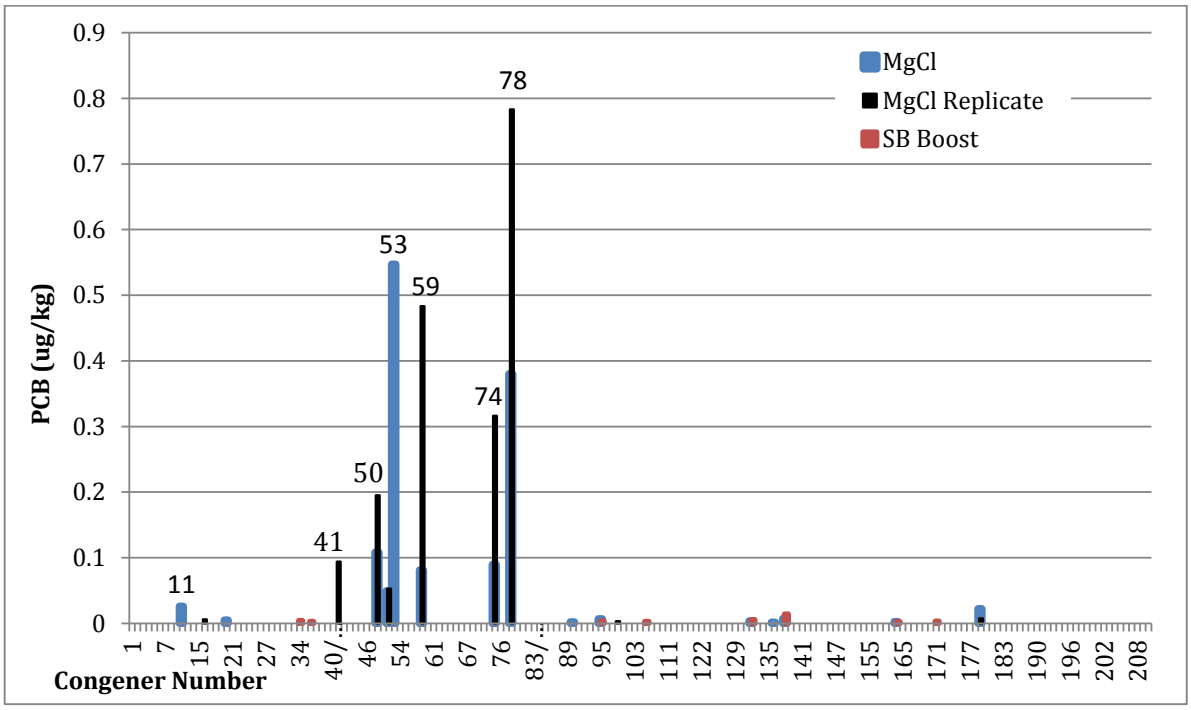

Figure 9. Deicer PCB Congeners

Antifreeze

Antifreeze mixtures may contain inadvertently generated PCBs, particularly those made with glycerol (also known as glycerin) synthesized from epichlorohydrine (Munoz, 2007). Kool Green Extended Life antifreeze was sampled, which contains a yellow color. The MSDS indicates that it contains ethylene glycol, diethylene glycol, and proprietary additives, inhibitors, and dye. The ethylene and diethylene glycols and glycerol have a similar chemical structure, but are not the same compound. Total PCB detected in the sample was **0.018 ug/kg**. Despite its yellow color, PCB-11 was not detected in the sample.

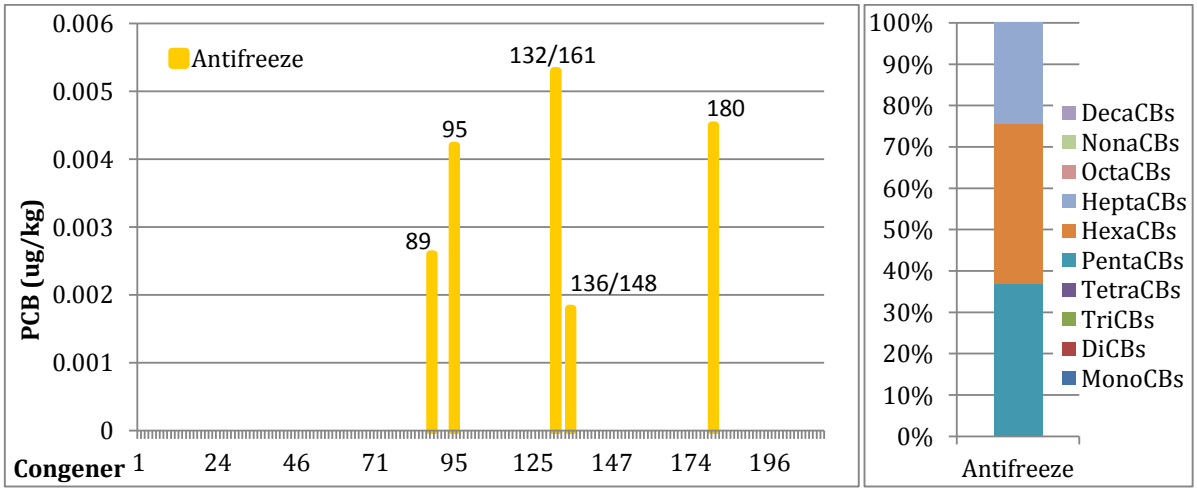

Figure 10. Antifreeze PCB Congeners and Homologue Patterns

Pesticides

Three types of pesticide and one adjuvant were sampled, including Weedar 64 (2,4-D formula), Portfolio 4F, Roundup Pro Max, and the adjuvant Crosshair. The chemical processes that make up chlorinated pesticides have been broadly determined by EPA to have a high potential for inadvertent PCB generation (Munoz, 2007).

PCBs were **non-detect** in the Weedar 64 sample and laboratory duplicate. None of the congeners were flagged for blank contamination. The main ingredients listed on the MSDS are 2,4-dichlorophenoxy acetic acid (2,4-D), dimethylamine salt, and trade secret inert ingredients. Interestingly, chemicals with similar structures to 2,4-D, including trichlorophenoxy acetic acid and dichlorophenyl acetic acid are listed as having the potential for inadvertent PCB generation, but 2,4-D is not (Munoz, 2007).

The total PCBs detected in the Portfolio 4F sample were **6.89 ug/kg**. The majority of this sample was composed of the coeluting congeners PCB-64 and 72. Sulfentrazone is the active ingredient in Portfolio 4F, making up about 40% of the product. Its chemical name is N-[2,4-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1H-1,2,4-triazol-1-yl]phenyl]methanesulfonamide. Other ingredients include toluene and propylene glycol.

Total PCBs detected in the Roundup Pro Max sample were **0.012 ug/kg**. The active ingredient, making up about 49% of the product, is potassium salt of N-(phosphonomethyl) glycine (potassium salt of glyphosate). Glycine is listed as a chemical product having the potential to contain inadvertently generated PCBs (Munoz, 2007).

The sample of the adjuvant Crosshair contained **0.316 ug/kg** total PCBs. It is composed of methyl ester, modified soybean oil. Soybean oil can be modified through a number of different processes. One option is to synthesize it from epoxidised soybean oil using methylene chloride (Xu et al., 2011). If this process was used, it could possibly be the pathway for inadvertent PCB generation because chlorine is introduced in the process. Glycerine is also a byproduct of this process, which is also listed as a potential inadvertent PCB generating substance when a chlorinated compound is used (Munoz, 2007). Figure 11 shows the congeners detected in the pesticide and adjuvant samples.

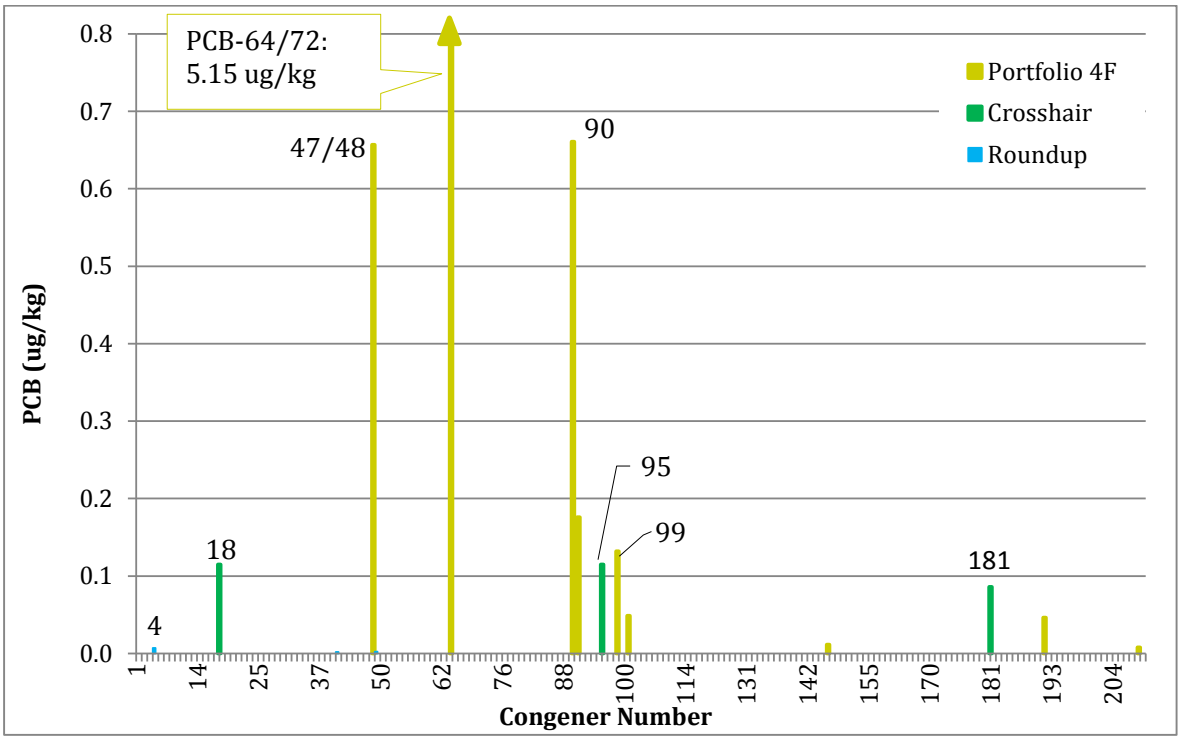

Figure 11. Pesticide and Adjuvant Congeners

Motor Oil and Lubricant

The Fleet Maintenance department primarily uses ConocoPhillips Firebird SAE 15W-40 Heavy Duty EC oil to maintain the City's vehicle fleets. This oil is made from greater than 50% re-refined base stocks. Because this same oil is used in many vehicles and serviced at the same shop, there was an opportunity to sample the same type of oil both before use and after an oil change for comparison. Additionally, Valvoline Full Synthetic SAE 5W-30 was sampled off-the-shelf from a local automotive store. This oil was sampled by the City in 2011 and contained the greatest concentration of PCBs of the oils sampled (see Table 2). A lubricant, MP Gear Lube SAE 85W-140 by Phillips 66 was also sampled. Total motor oil and lubricant PCB concentrations sampled in 2014 are shown in Table 6.

Table 6. Motor Oil and Lubricant Total PCBs

Sample	Total PCB (ug/kg)
Firebird 15-40 Bulk	0.856
Used Firebird 15-40 Bulk	0.502
Used Firebird 15-40 Bulk Replicate	2.375
Valvoline Full Synthetic 5-30	0.969
Gear Lube	0.623

There was a wide range of PCB congener distribution for the various oil and lubricant samples. Most of the congeners were in the low to mid chlorinated range. The used Firebird motor oil sample and its duplicate were not similar to each other in total PCB concentration or congener distribution as a result of its heterogeneity.

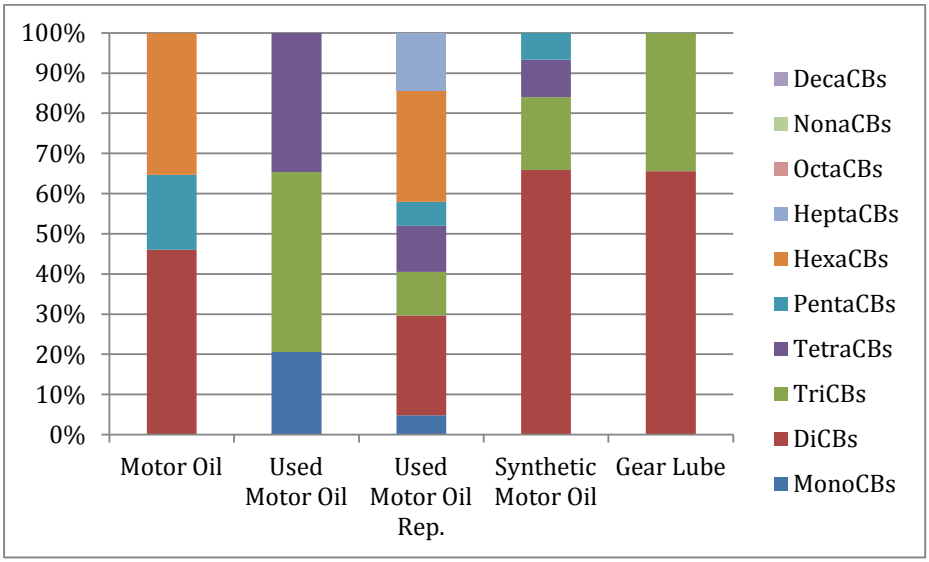

Figure 12. Motor Oil and Lubricant PCB Homologue Patterns

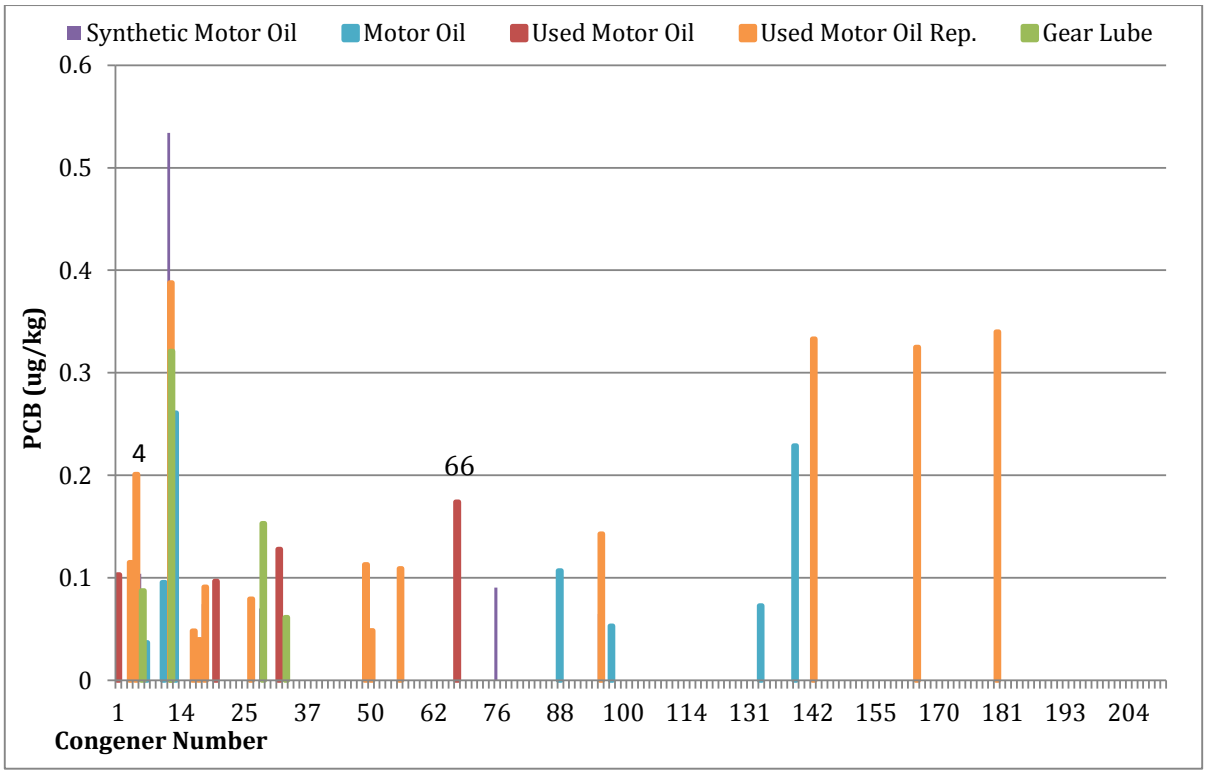

Figure 13. Motor Oil and Lubricant PCB Congeners

Gasoline and Diesel

Regular unleaded gasoline and #2 dyed diesel were sampled from the fuel tanks at the City's Riverside Park Water Reclamation Facility. The diesel sample was non-detect. During laboratory analysis, coextracting interferences resulted in the detection limits being raised to 2 ug/kg for each of the monoCB, diCB, and triCB congeners. Therefore, PCBs may still be present in diesel at less than 2 ug/kg per congener, but were unable to be detected due to interferences.

The total PCBs for the gasoline sample was **0.935 ug/kg**. Nearly all of the sample was composed of PCB-2 (0.93 ug/kg). The remainder was the coeluting congeners PCB-138 and 160.

Dust Suppressant

The City of Spokane has some unimproved roads that have not been paved and require dust control. Three forms of dust control approved for use in the City are magnesium chloride (at a different concentration than the deicer), emulsified asphalt dust abatement (EADA), and lignosulfonate. Samples were collected from each of these three dust suppressants.

The magnesium chloride dust suppressant brand is DustGard, made from naturally occurring minerals from the Great Salt Lake. EADA is a petroleum-based product, containing primarily petroleum asphalt and petroleum bitumen with water and a proprietary mix of petroleum distillates, polymer modifier, surfactants, emulsifier, and other additives. Ligno Road Binder lignosulfonate is derived from natural polymers in wood, and contains sucrose, plant fiber, and an aquatic solution according to its MSDS.

Table 7. Dust Suppressant Total PCBs

Sample	Total PCB (ug/kg)
EADA	0.091
Lignosulfonate	0.086
Magnesium Chloride	3.574

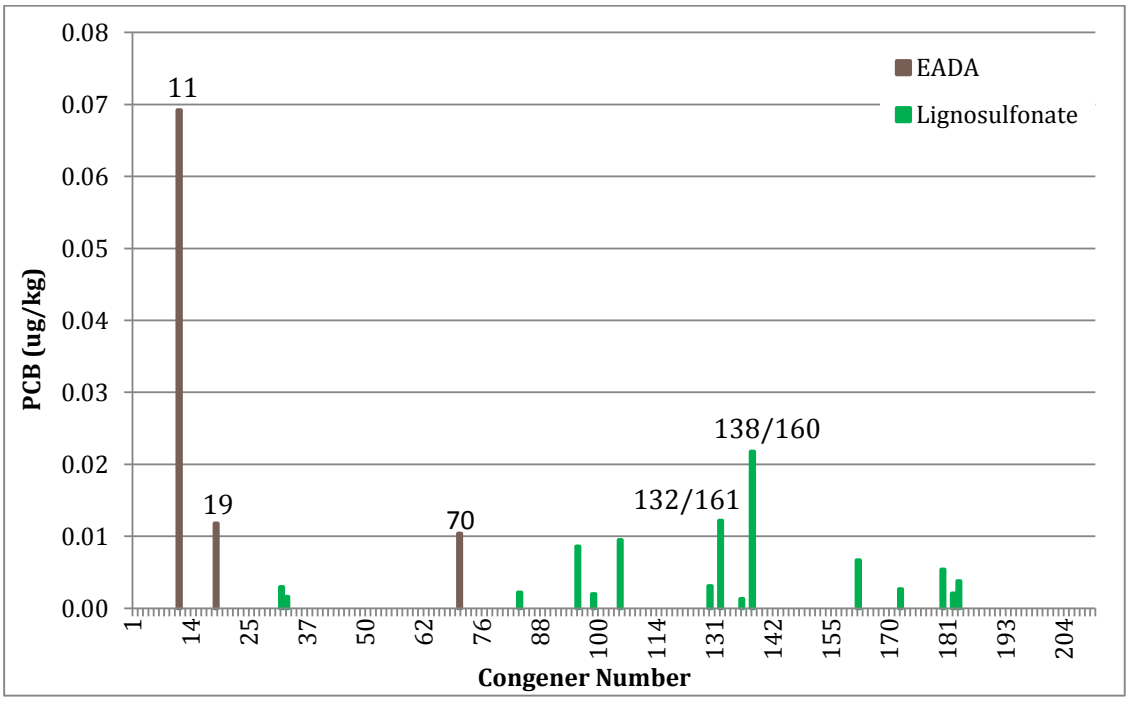

Figure 14. EADA and Lignosulfonate Congeners

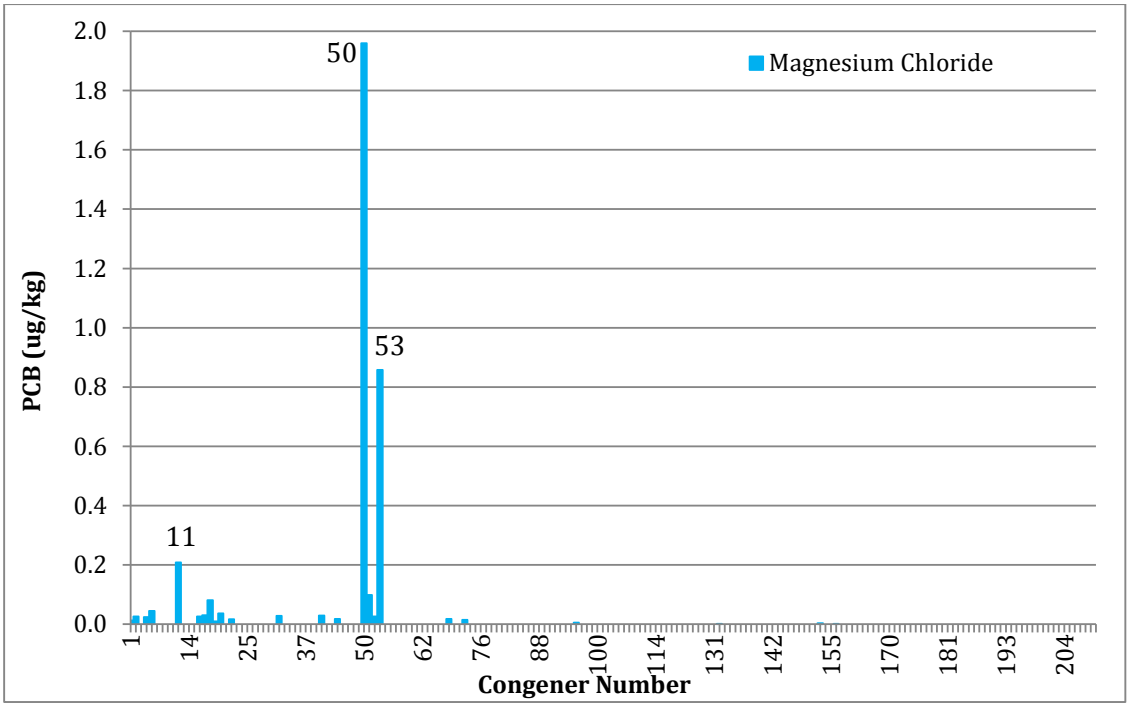

Figure 15. DustGard Magnesium Chloride Congeners

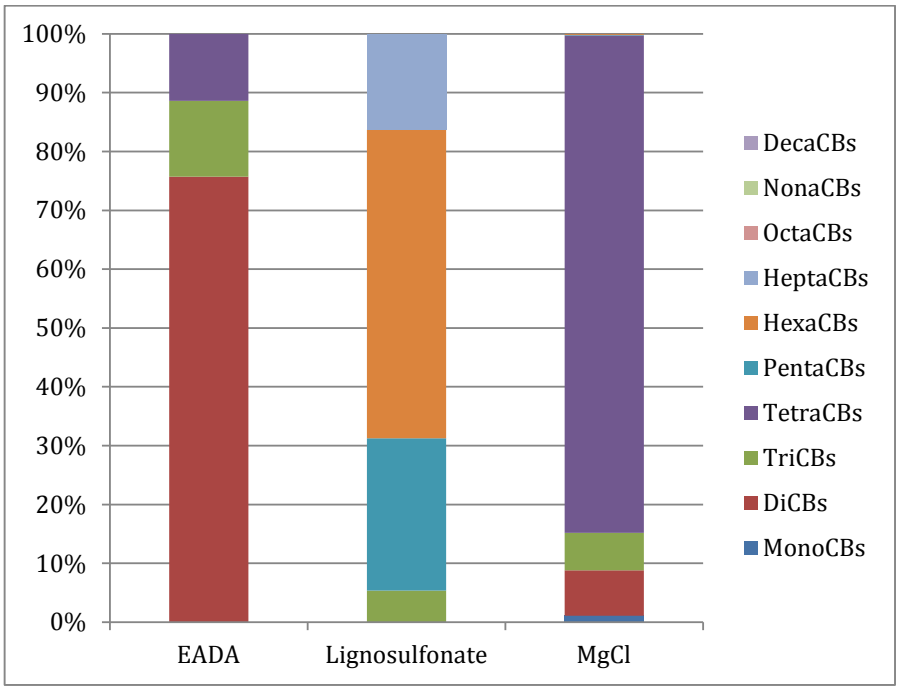

Figure 16. Dust Suppressant Homologue Patterns

The homololgue pattern for EADA is similar to synthetic oil (Figure 12), dominated by diCBs with lesser percentages of triCBs and tetraCBs. Lignosulfonate has a somewhat similar homologue pattern to Aroclor 1260, but the individual congener patterns don't match up well (see Appendix A).

Asphalt Related Products

The asphalt products that were sampled include asphalt tack, crack sealer, and an asphalt release agent. Asphalt tack is made of an asphalt emulsion, and is placed between old and new asphalt layers to adhere them to one another. The crack sealer, SA Premier, is made of asphalt, vacuum distillate, petroleum distillate, styrene-butadiene block copolymer, vulcanized rubber compound, mineral filler, methyl methacrylate, and linear low density polyethylene. The asphalt release agent brand is Soy What by TechniChem, and is "crafted from a by-product that is extracted from soybeans," according to the technichemcorp.com website. Total PCBs and congener and homologue patterns are shown in the following table and figures.

Table 8. Asphalt Related Product Total PCBs

Sample	Total PCB (ug/kg)
Asphalt Tack	0.085
Crack Sealer	7.975
Asphalt Release Agent	0.558

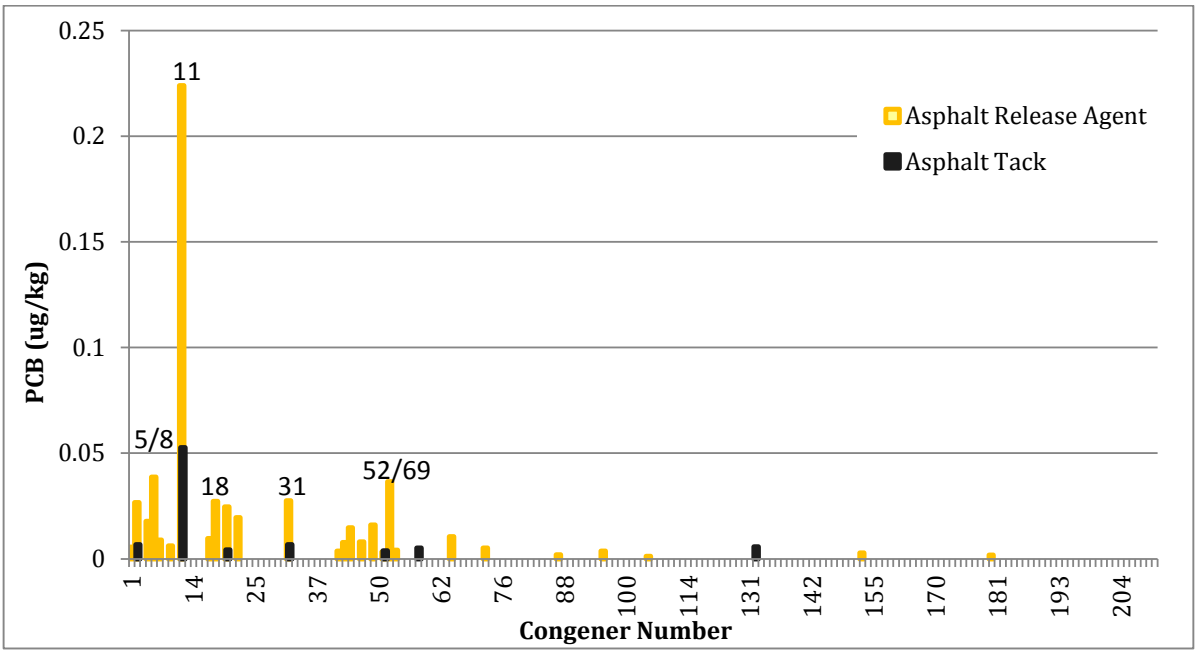

Figure 17. Asphalt Release Agent and Tack Congener Patterns

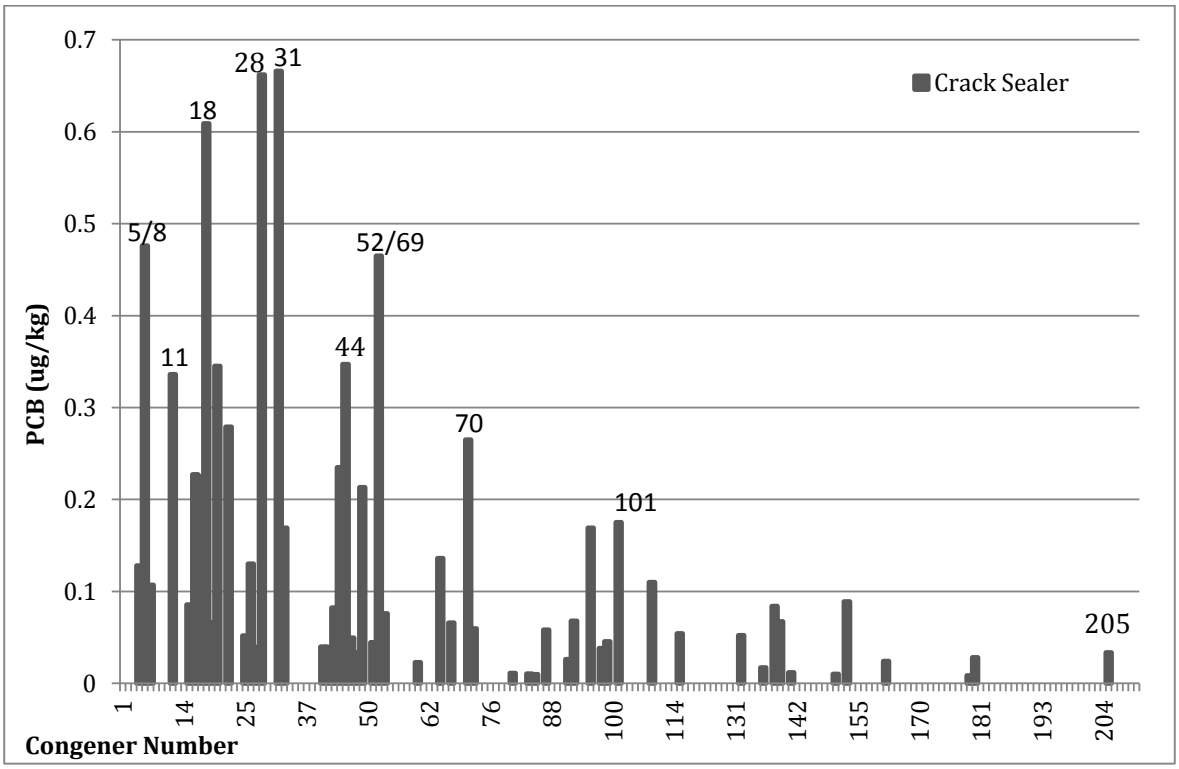

Figure 18. Crack Sealer Congener Pattern

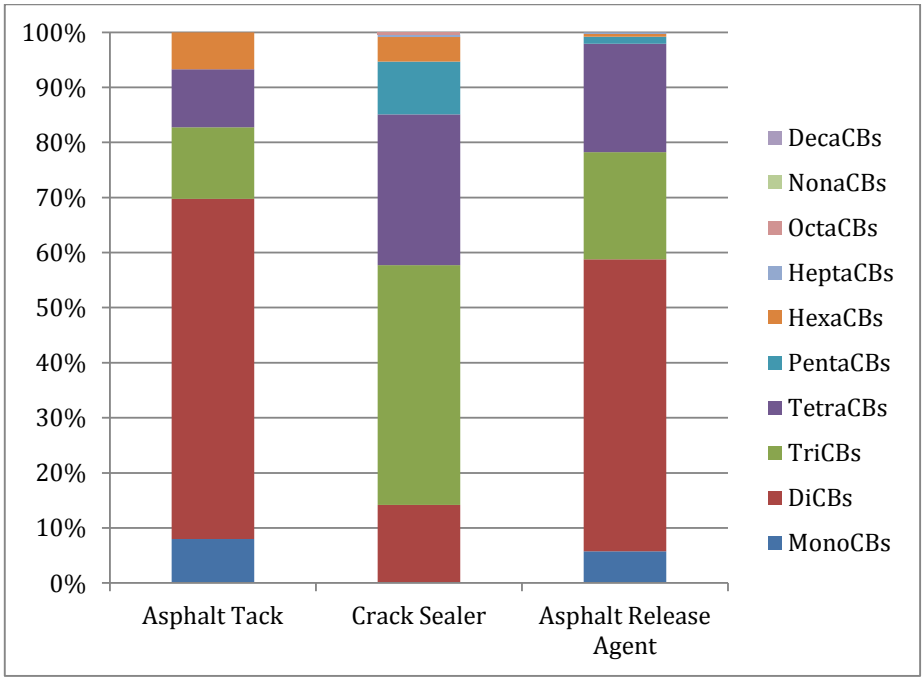

Figure 19. Asphalt Product Homologue Patterns

The crack sealer has a similar congener and homologue pattern to Aroclor 1242. The congeners from the crack sealer sample were converted to percent of total PCB by weight and are plotted against Aroclor 1242 in the same units in Figure 20. Aroclor 1242 had a wide variety of end uses, one of them being in rubbers. One of the ingredients in the crack sealer is vulcanized rubber compound. PCB-11 was detected at over 4% of the crack sealer PCB composition, but is not present in most Aroclor mixes.

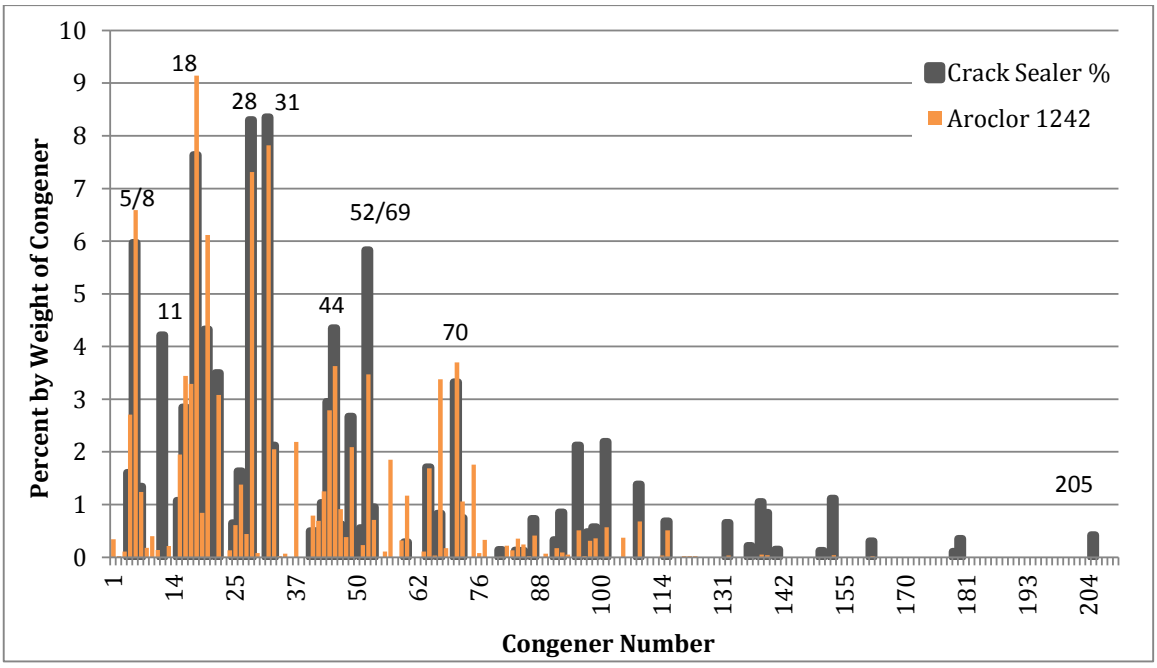

Figure 20. Crack Sealer and Aroclor 1242 Congener Distributions

Hydroseed

A hydroseed mix was sampled due to the prevalent use of hydroseed in roadside projects and its typical green coloring. The sample was collected from a new 50 pound bag of Nature's Own Hydromulch, which was not yet mixed with seed, fertilizer, or other additive. The Nature's Own Hydromulch MSDS indicates that it is composed of primarily wood fiber material with green liquid and a surfactant. The sample contained shredded colored newspaper cellulose. Total PCBs detected in the sample was **2,509 ug/kg**. The following figures show the congeners detected and homologue patterns for the sample.

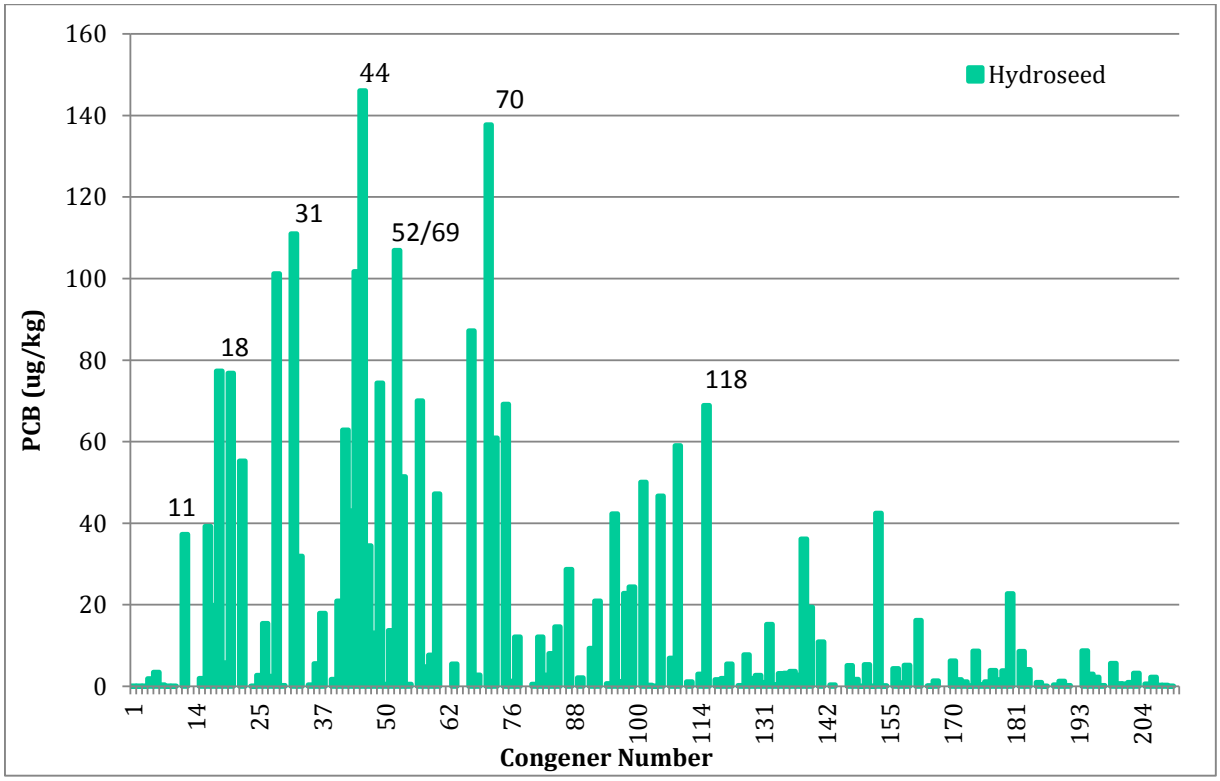

Figure 21. Hydroseed Congeners

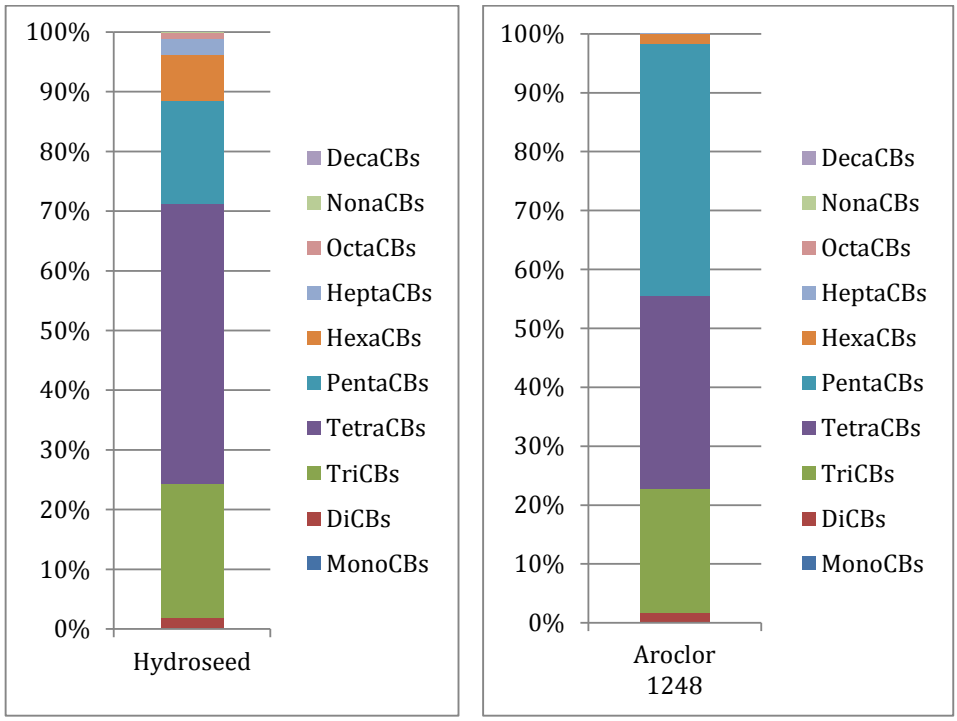

Figure 22. Hydroseed and Aroclor 1248 Homologue Patterns

In an unrelated incident, a landscape contractor received a penalty from the State of Iowa for illegally discharging a hydroseed mixture on the bank of a creek (Scriven-Young, 2010). The hydroseed contained 320 parts per billion of Aroclor 1248 as well as the pesticides DDT and DDE. Interestingly, the sample collected by the City of Spokane has a homologue pattern very similar to that of Aroclor 1248.

The hydroseed congeners from the City's sample were converted to percent of total PCB by weight and are plotted against Aroclor 1248 in the same units in Figure 23 below. The two congener patterns are quite similar. Note that PCB-11 is present in the hydroseed, but not the Aroclor. This indicates a secondary source of PCBs from pigment that is relatively minor compared to the Aroclor.

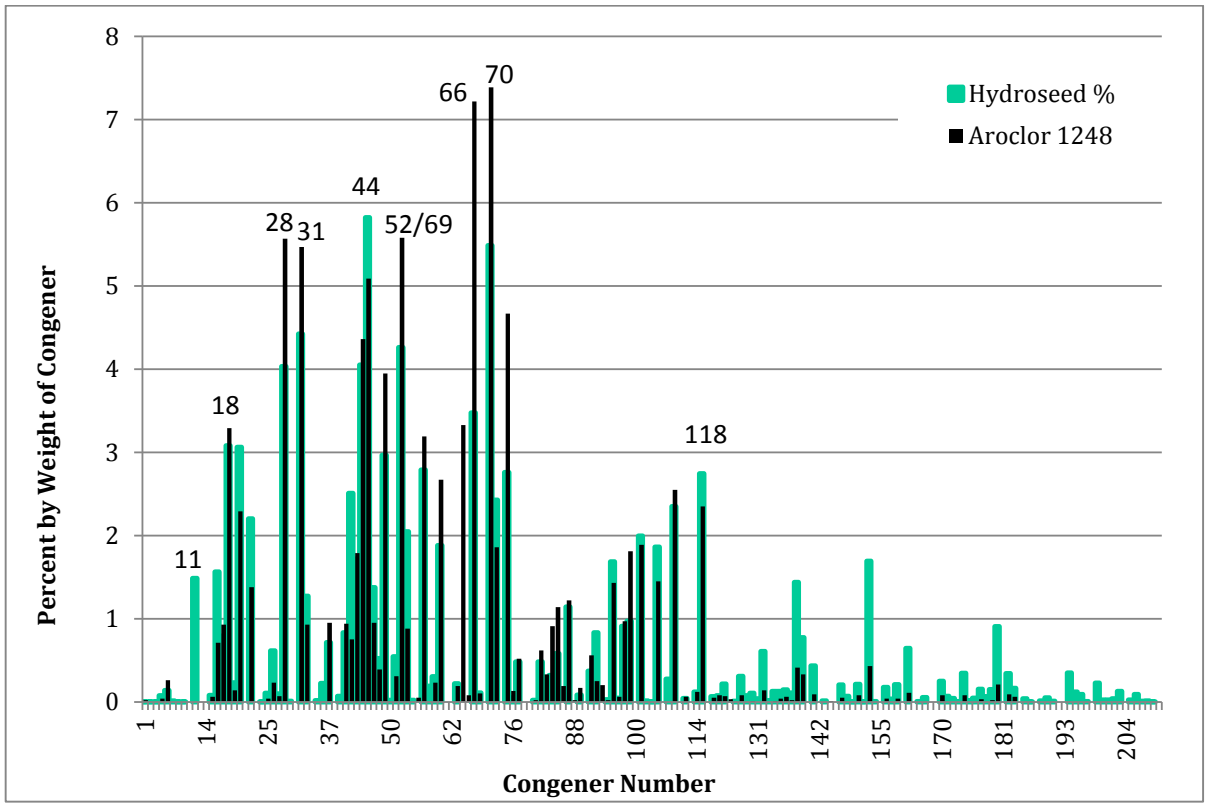

Figure 23. Hydroseed and Aroclor 1248 Congener Distributions

Pipe Material

There are hundreds of miles of PVC pipe used in the City's sanitary and storm sewer systems. Dischargers in the Spokane region have been collecting sanitary and stormwater samples for ultra low-detection PCB analysis, and many of these samples have traveled through miles of PVC pipe prior to collection. In an effort to screen the potential for PCB contribution from pipe material, PVC pipe, cast in place pipe (CIPP) liner and shortliner pipe repair materials were sampled.

The type of PVC sampled was ASTM 3034 collected from a new, unused eight-inch diameter pipe. CIPP is constructed from a felt tube saturated with resin and coated with polyurethane, and is cured inside an existing pipe. The section of CIPP liner sent in for analysis was originally collected from a construction project in northeast Spokane in April, 2013. It was kept in an office environment and not exposed to the elements after that time. Shortliner pipe repair is constructed in the same way, and made of a polyester-fiberglass liner impregnated with thermosetting epoxy resin. A test section of shortliner was cured in a new pipe on the ground surface at the City's Sewer Maintenance Department in October, 2014 for use in this sampling study.

Pieces of pipe were sent to the laboratory for analysis to help determine the PCB content in the material itself. The potential for PCBs to leach from the pipe material to stormwater and sanitary

sewage is outside the scope of this project, but future analysis is warranted based on the results shown in Table 9.

Table 9. Pipe and Pipe Repair Material Total PCBs

Material	Total PCB (ug/kg)
PVC (ASTM 3034) Pipe	1.999
CIPP Liner	1.110
Shortliner	17.780

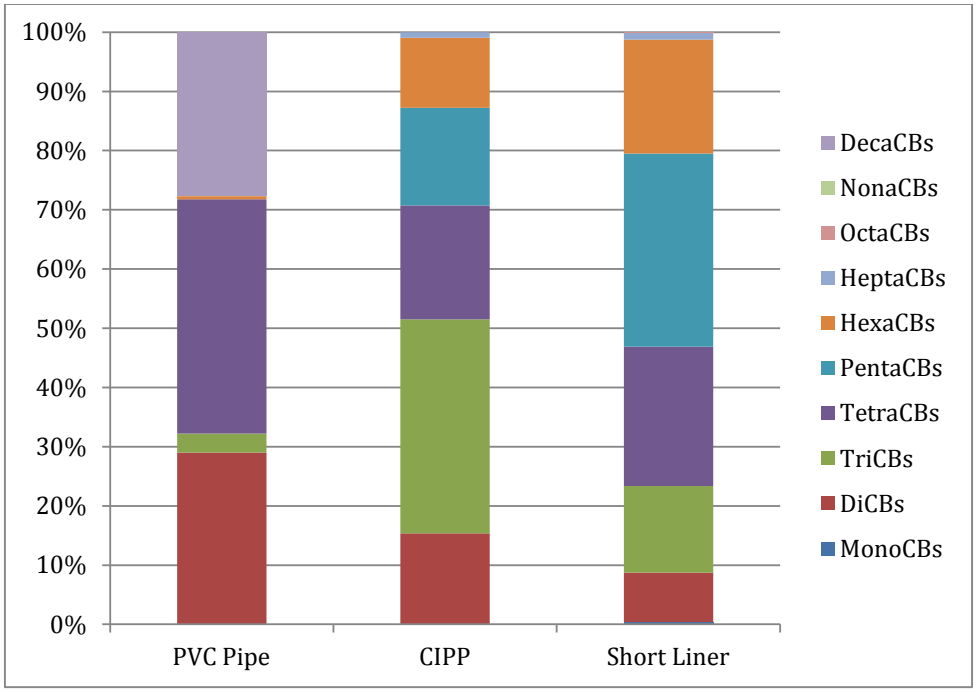

Figure 24. Pipe Material Homologue Patterns

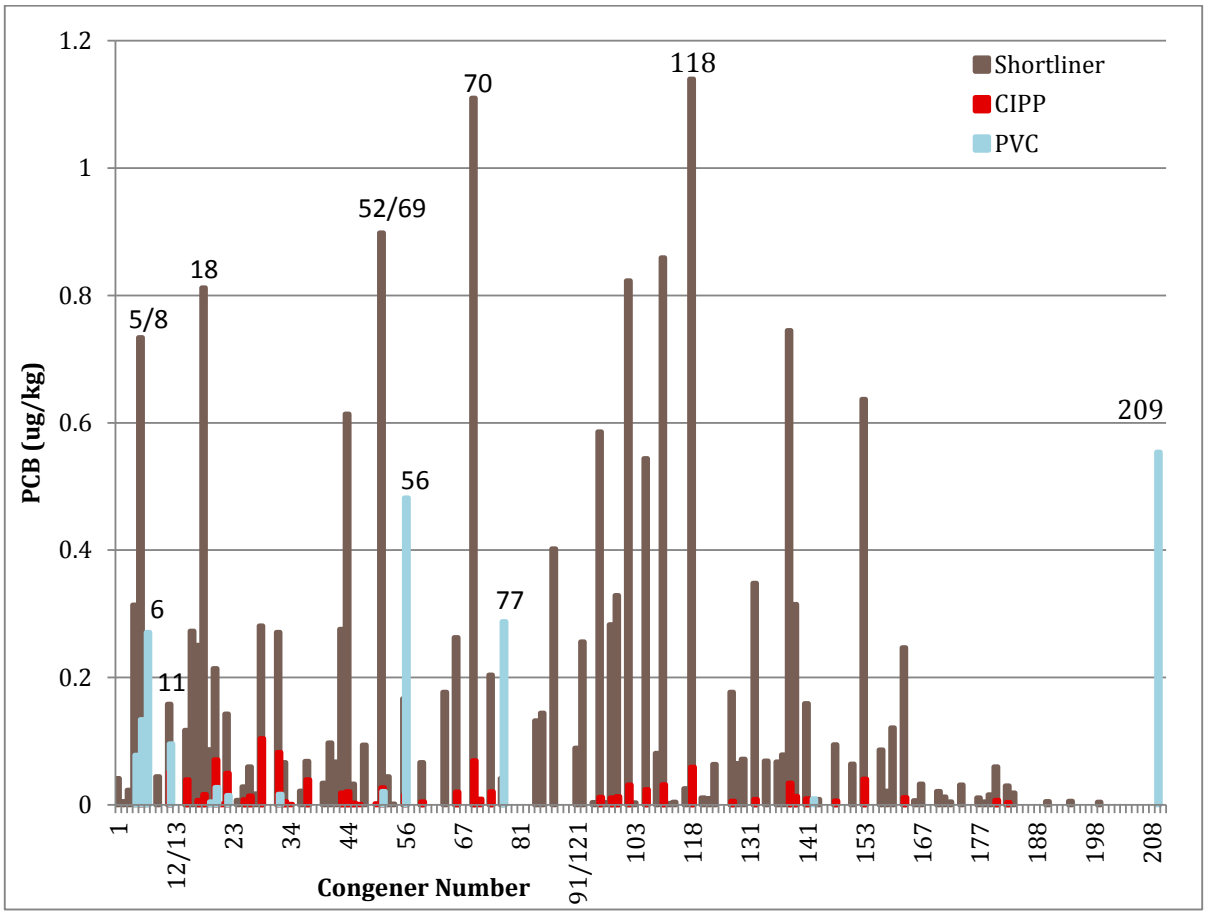

Figure 25. Pipe Material PCB Congeners

Figure 25 shows congener patterns for the sampled pipe materials. Congener distributions (percent of total PCB) for the pipe materials were then compared to congener patterns for Aroclors. The PVC and CIPP samples did not appear to correlate with Aroclor patterns. The Shortliner sample appears to correlate somewhat with a combination of two or more Aroclors. Specifically, a combination of both Aroclors 1242 and 1248 matches the shortliner sample the most closely (Figure 26).

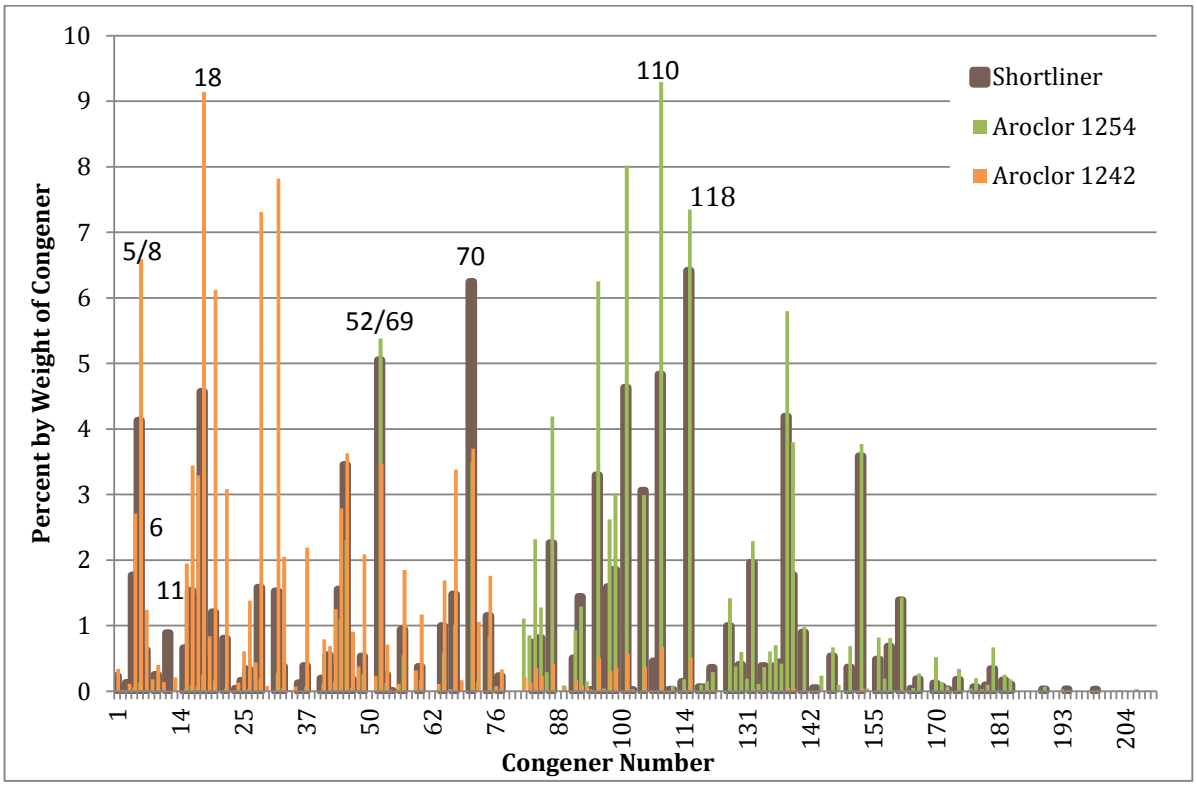

Figure 26. Shortliner Congener Distribution Compared to Aroclors 1242 and 1254

Firefighting Foam

Discharges from emergency firefighting activities are an exempt activity under the Phase II Eastern Washington Municipal Stormwater Permit. However, these discharges can easily enter a storm sewer system without proper containment and contribute contaminants to the environment. Alcoseal 3-3 Class B firefighting foam was sampled. Ingredients listed on the MSDS sheet include hydrolyzed protein, fluorosurfactants, 1,2 benzoisothiazelin, and hexylene glycol. The total PCB concentration was **0.029 ug/kg**. The associated congener and homologue patterns are shown in Figure 27.

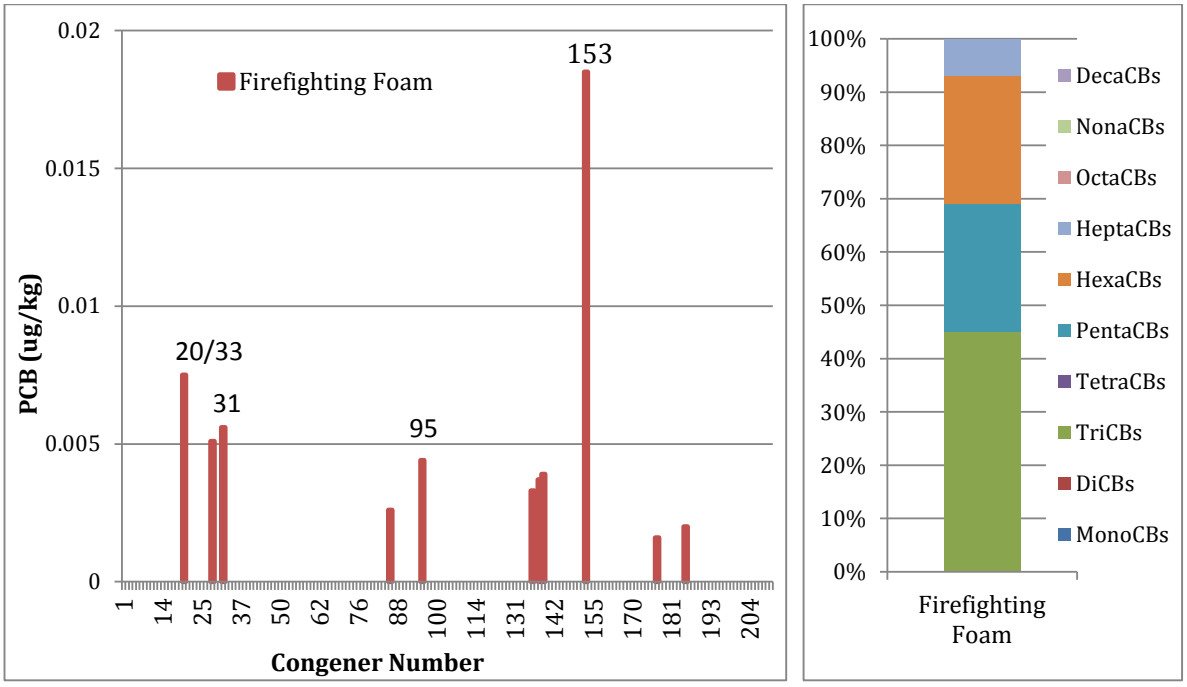

Figure 27. Firefighting Foam PCB Congeners and Homologue Pattern

Cleaners and Degreasers

Inadvertent PCB generation is possible with the manufacture of soaps, detergents, surfactants, and degreasers (Munoz, 2007). A detergent made by Hotsy was sampled as well as Simple Green degreaser.

The Hotsy Super XL detergent contained **0.003 ug/kg** total PCBs. A laboratory duplicate was analyzed, containing 0.068 ug/kg total PCBs. This product contains trisodium phosphates, alkaline builders, and surfactants. Congener distributions from the primary sample are shown in the figure below, containing only PCB-36.

The Simple Green degreaser contained **0.068 ug/kg** total PCBs, with nearly half of this total from PCB-11. The ingredients consist of primarily water with 2-butoxyethanol, ethoxylated alcohol,

tetrapotassium pyrophosphate, sodium citrate, and a proprietary mix of fragrance and polymeric colorant.

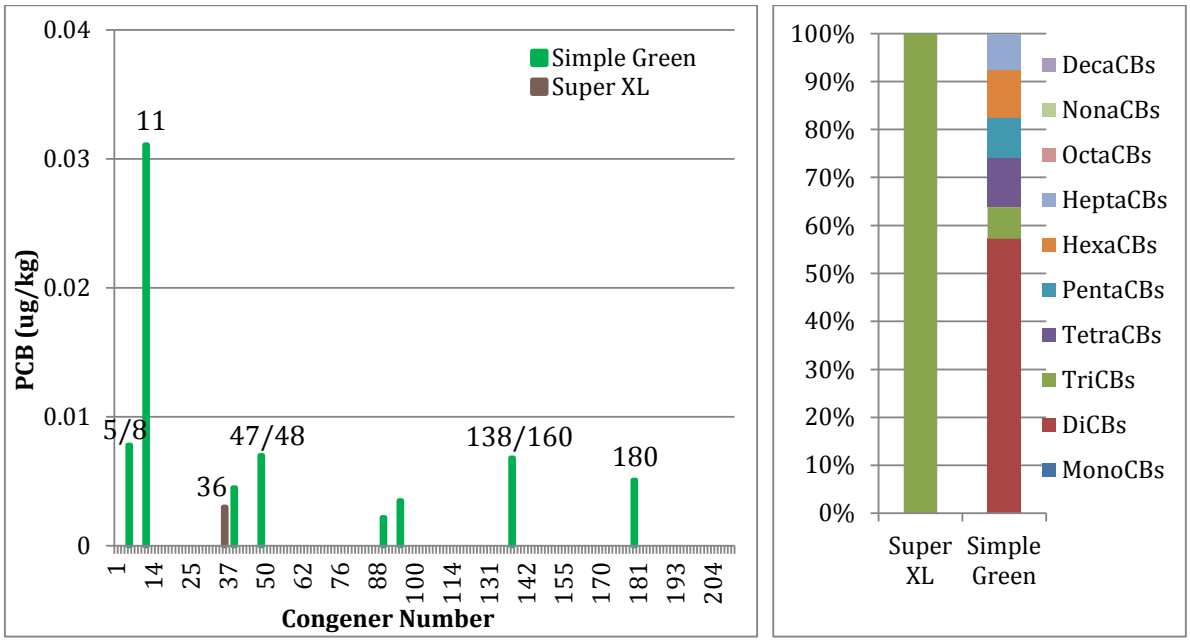

Figure 28. Simple Green and Super XL PCB Congeners and Homologue Pattern

Personal Care Products

Sampling in the storm and sanitary sewer systems over the past several years has indicated that total PCB concentrations in the sanitary sewer collection system are slightly greater than average concentrations in stormwater. So, in addition to products that can contribute PCBs to stormwater, five personal care products that may contribute PCBs to the sanitary sewer collection system were sampled. The products sampled were liquid and contained pigments. Table 10 shows the product brands sampled, total PCBs, pigments listed in the ingredients, and the so-noted 'ingredients of interest.' Many of these products have a long list of ingredients. Those ingredients that are chlorinated, contain benzene rings, or are suspected to be associated with inadvertent PCB production based on the literature search are included in Table 10 as ingredients of interest.

Table 10. Personal Care Products

Brand	Total PCB (ug/kg)	Ingredients of Interest	Pigments
Dial Antibacterial hand soap (pomegranate and tangerine)	0.037	Triclosan, tetrasodium EDTA, sodium chloride, polyquaternium-7	Yellow 6, Red 33, Red 40

Brand	Total PCB (ug/kg)	Ingredients of Interest	Pigments
Tide Original laundry detergent	0.174	Ethanolamine, Benzene sulfonic acid (sodium salt and monoethanolamine salt), disodium diaminostilbene disulfonate, dimethicone (type of silicone)	Liquitint® Blue HP (Polymeric colorant)
Dawn Ultra antibacterial dish soap	0.083	Chloroxylenol, sodium chloride	Yellow 5, Blue 1
Suave Naturals shampoo	0.058	Tetrasodium EDTA, ammonium chloride, methylchloroisothiazolinone	Blue 1, Red 33
Aquafresh Extreme Clean Whitening toothpaste	0.032	Glycerin, titanium dioxide, sodium saccharin	Red 30

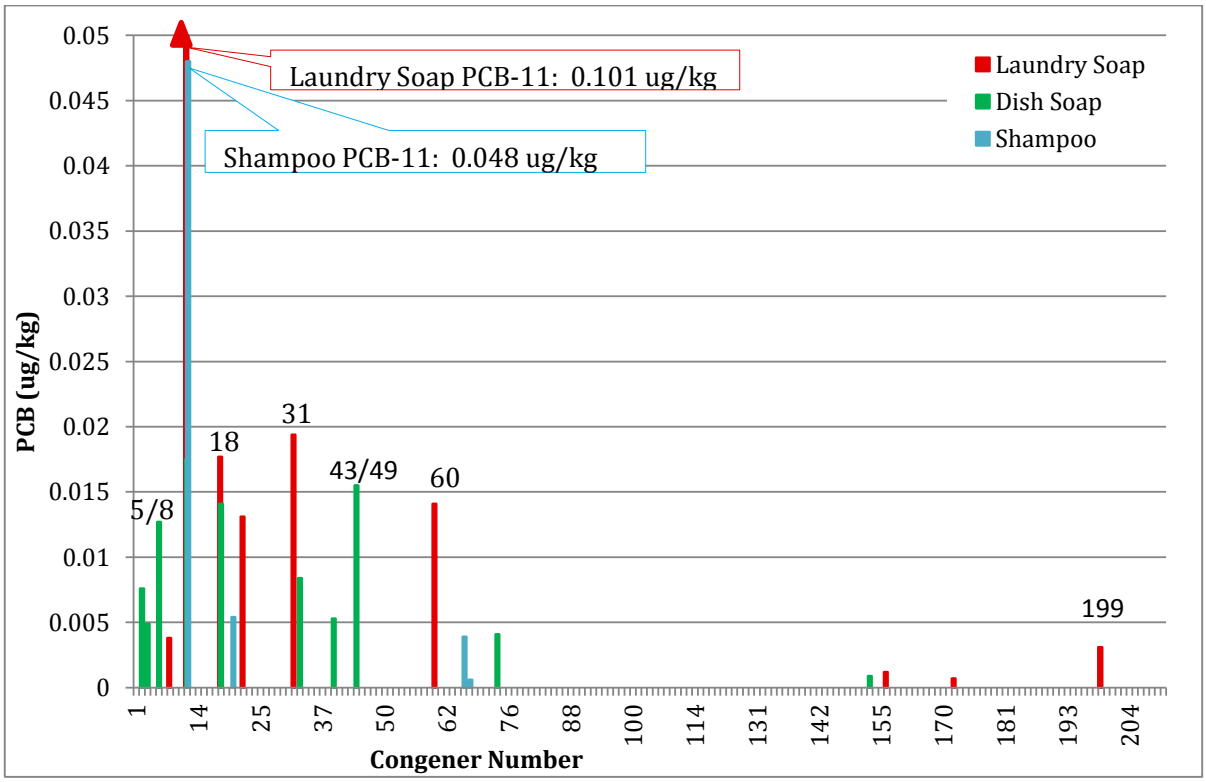

Figure 29. Laundry Soap, Dish Soap, and Shampoo Congeners

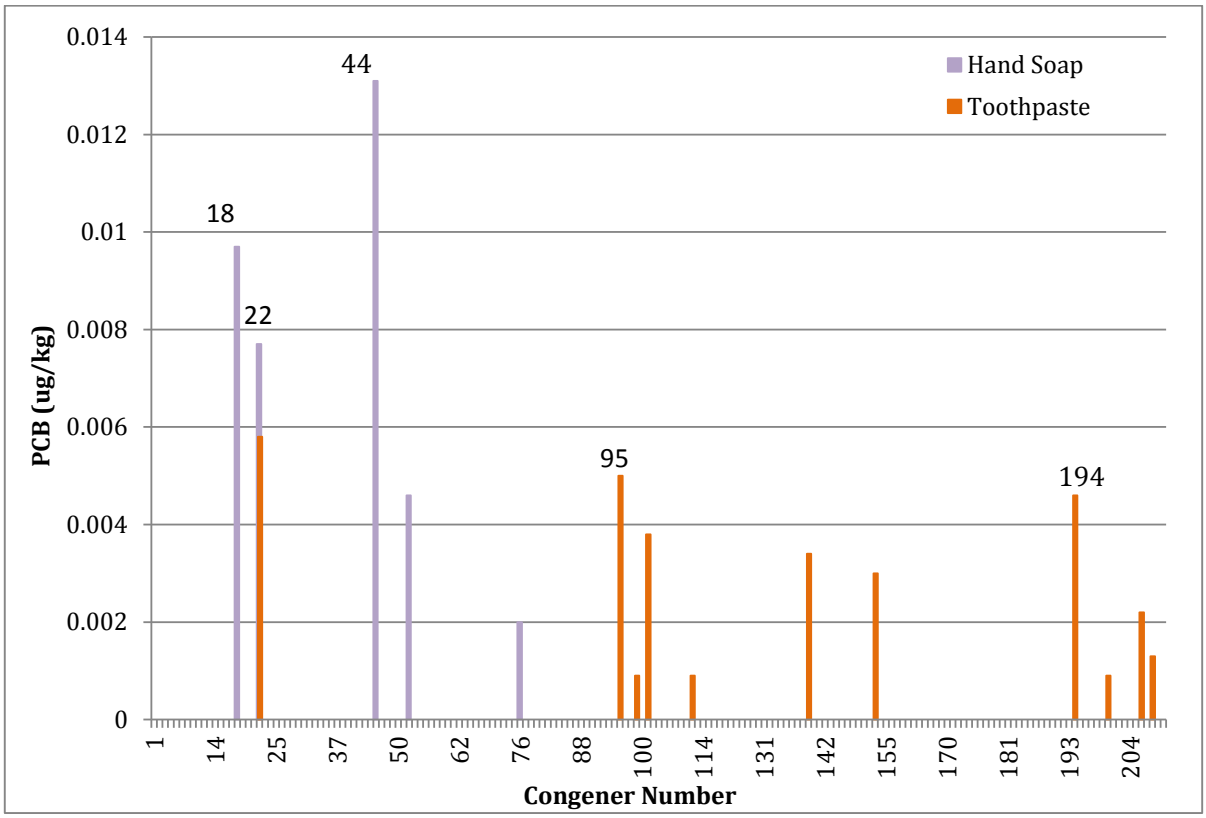

Figure 30. Hand Soap and Toothpaste Congeners

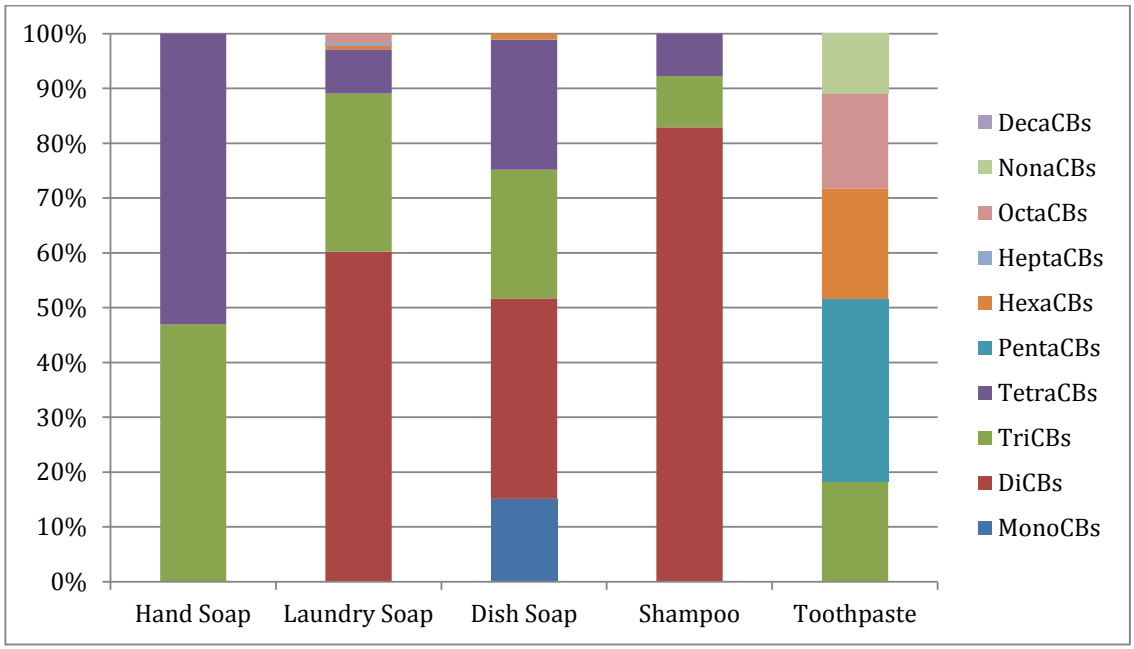

Figure 31. Personal Care Product Homologue Patterns

CONCLUSIONS

PCBs were detected in 39 of the 41 product samples, with a wide range of congener patterns. Figure 32 shows the frequency of detection of each congener in this study. The congeners most frequently detected are the coeluting congeners PCB-52/69 (detected in 30 of the samples) followed by PCB-11 and PCB-28 (detected in 25 of the samples). PCB-52 is one of the most abundant congeners found in the environment, and is found in Aroclor mixtures from 0.1% to 5.6% of the mixture by weight (Frame et. al, 1996). PCB-28 is also commonly found in Aroclor mixtures at up to 8.5% of the total mixture by weight (Frame et. al, 1996). Because PCB-11 was one of the most frequently detected congeners, and it is generally not found in Aroclor mixes, pigments are likely a common source of inadvertently produced PCBs in the products sampled.

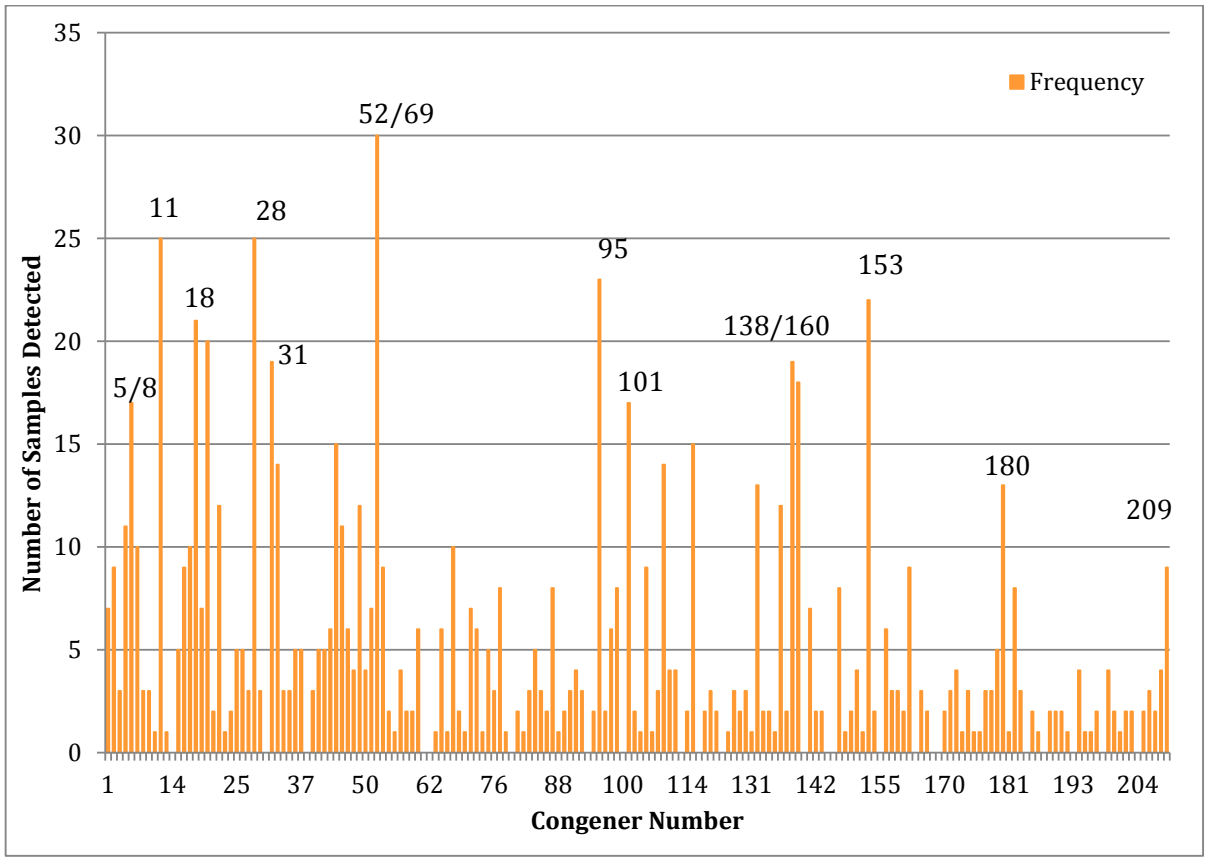

Figure 32. Frequency of Detections per Congener

The results from this report may be used for a number of PCB tracking and reduction activities. Additional research may be needed to determine potential pathways between some of the sampled products and stormwater. For PCB reduction activities, total PCB loading (volume of product used) should be assessed to aid in prioritization. Manufacturers may also be interested in exploring PCB-free alternatives where feasible.

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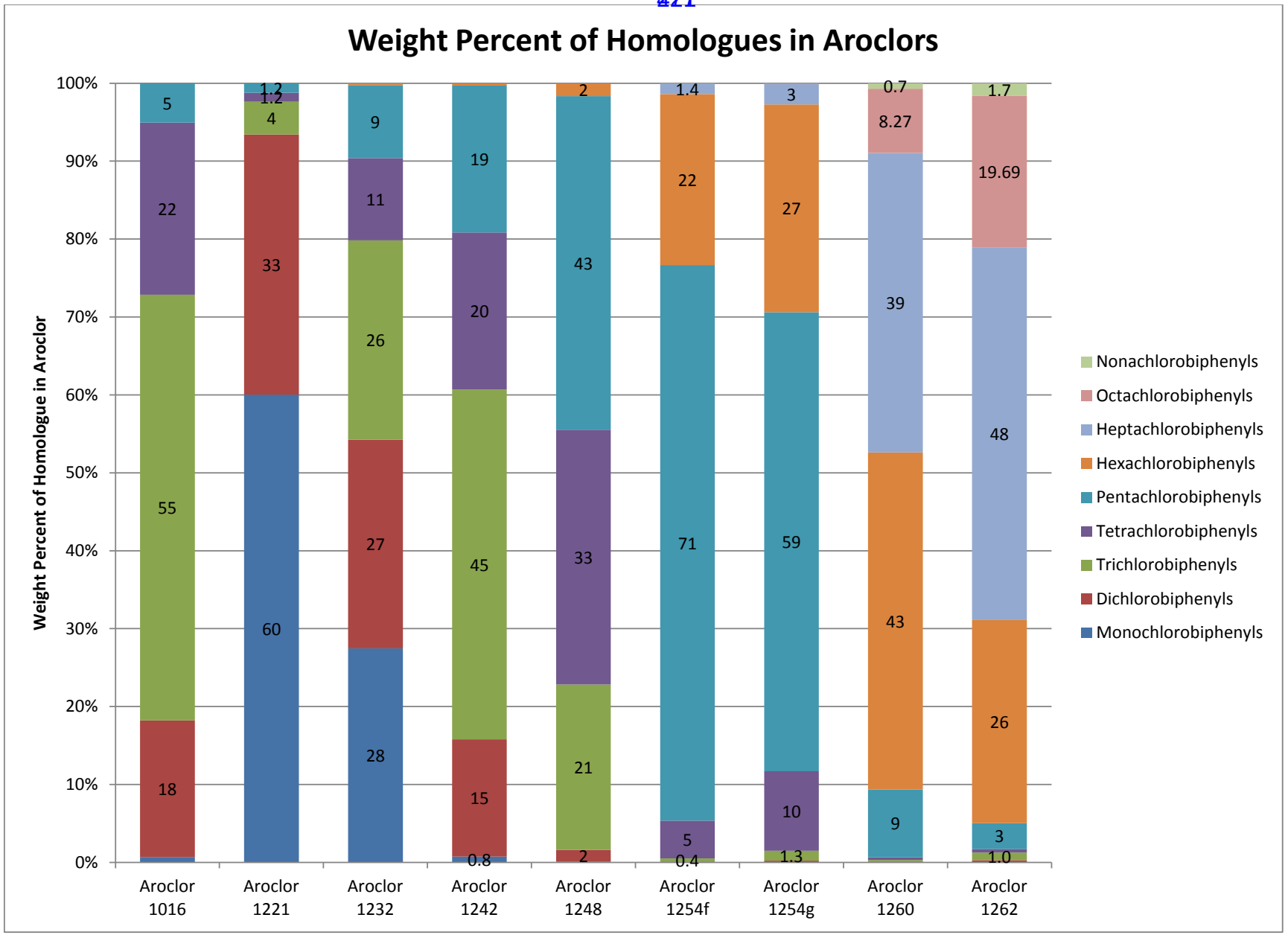
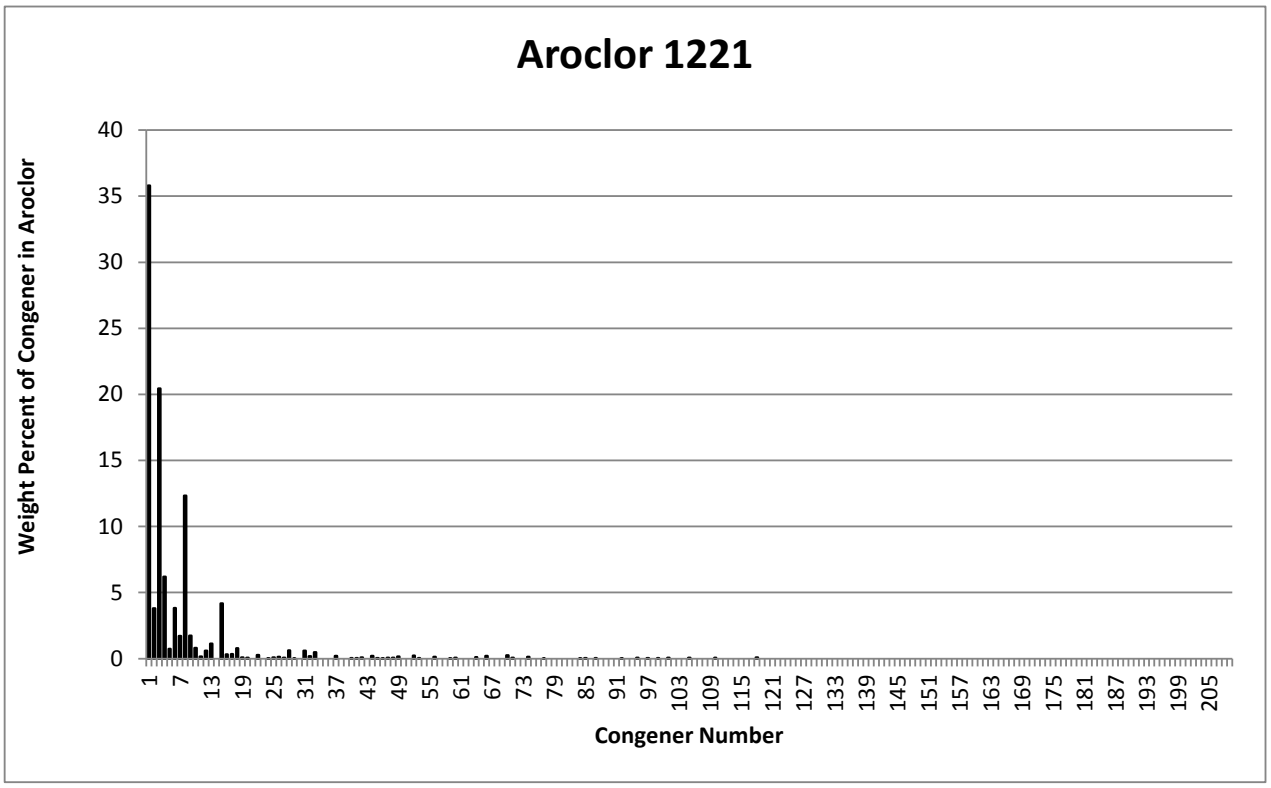
Appendix A

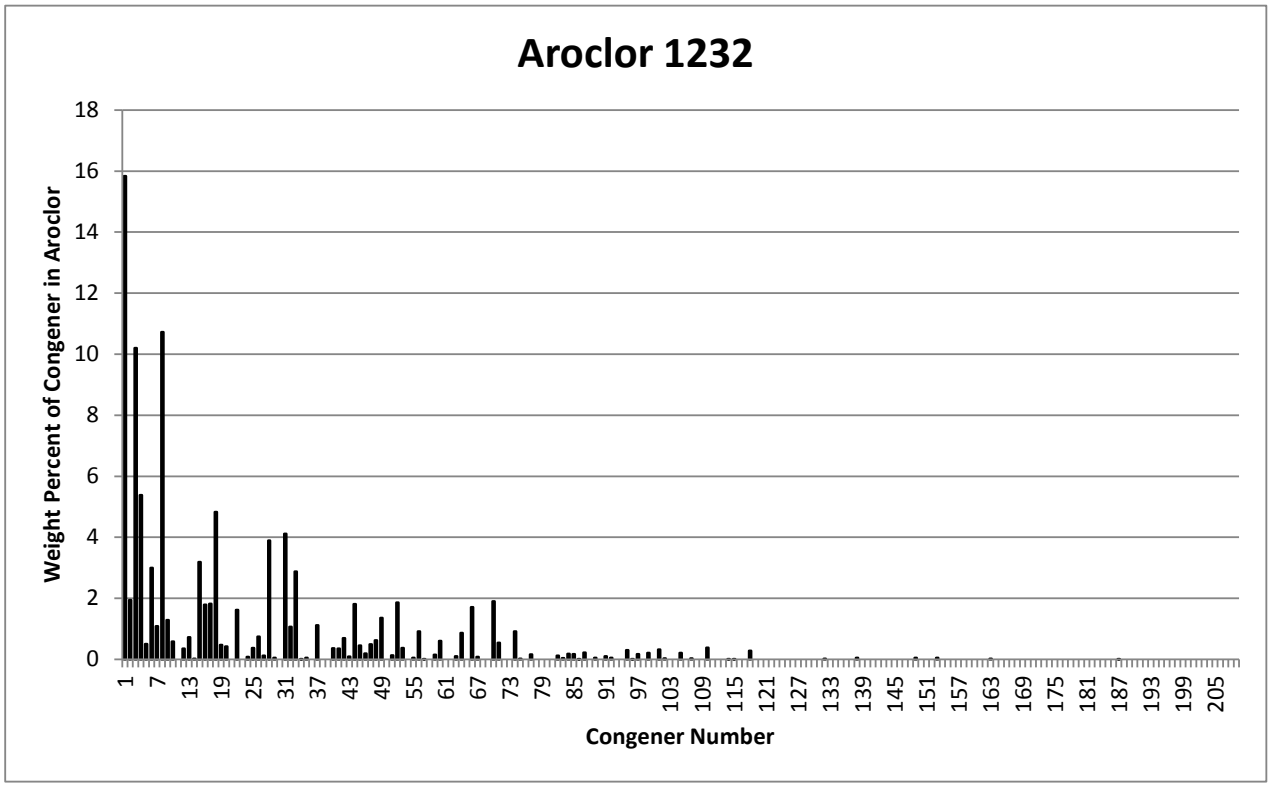
AROCLOR HOMOLOGUES AND CONGENERS

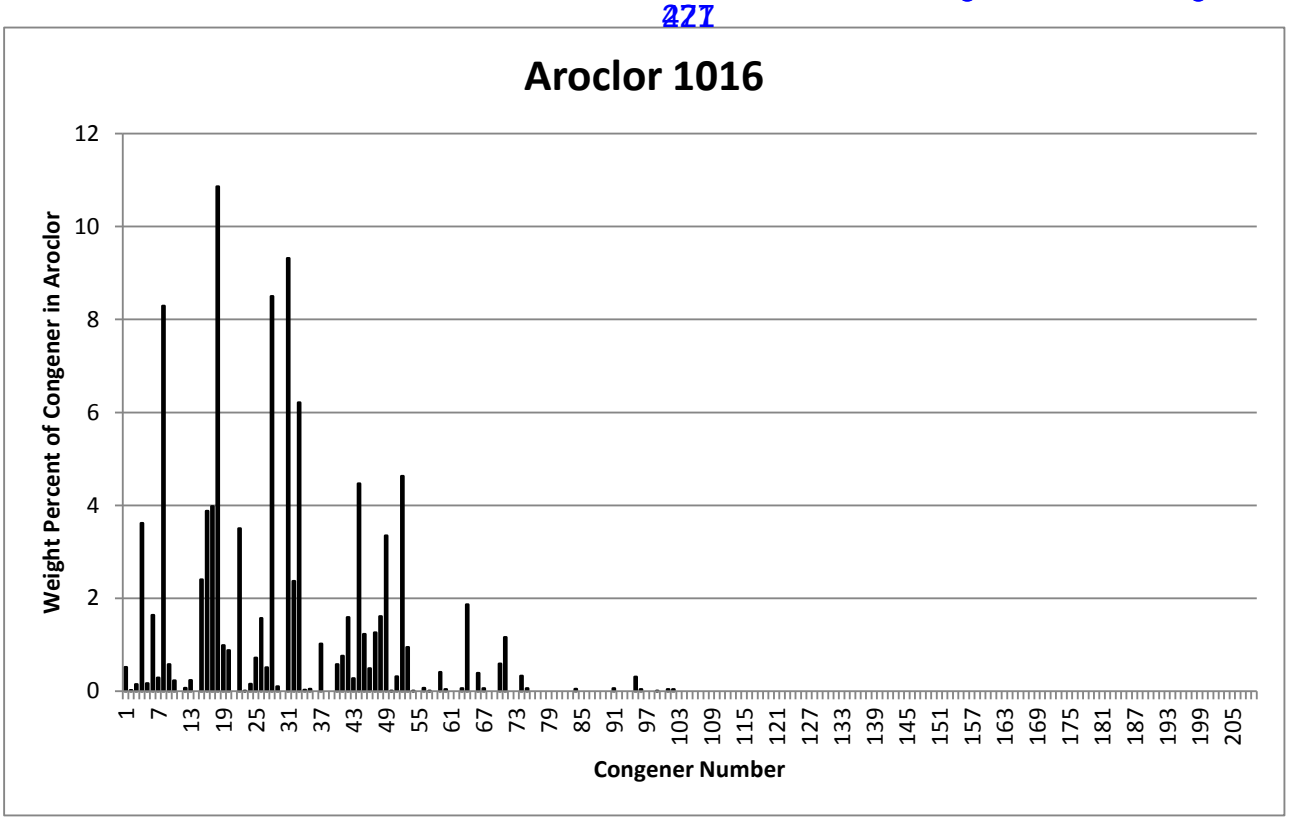


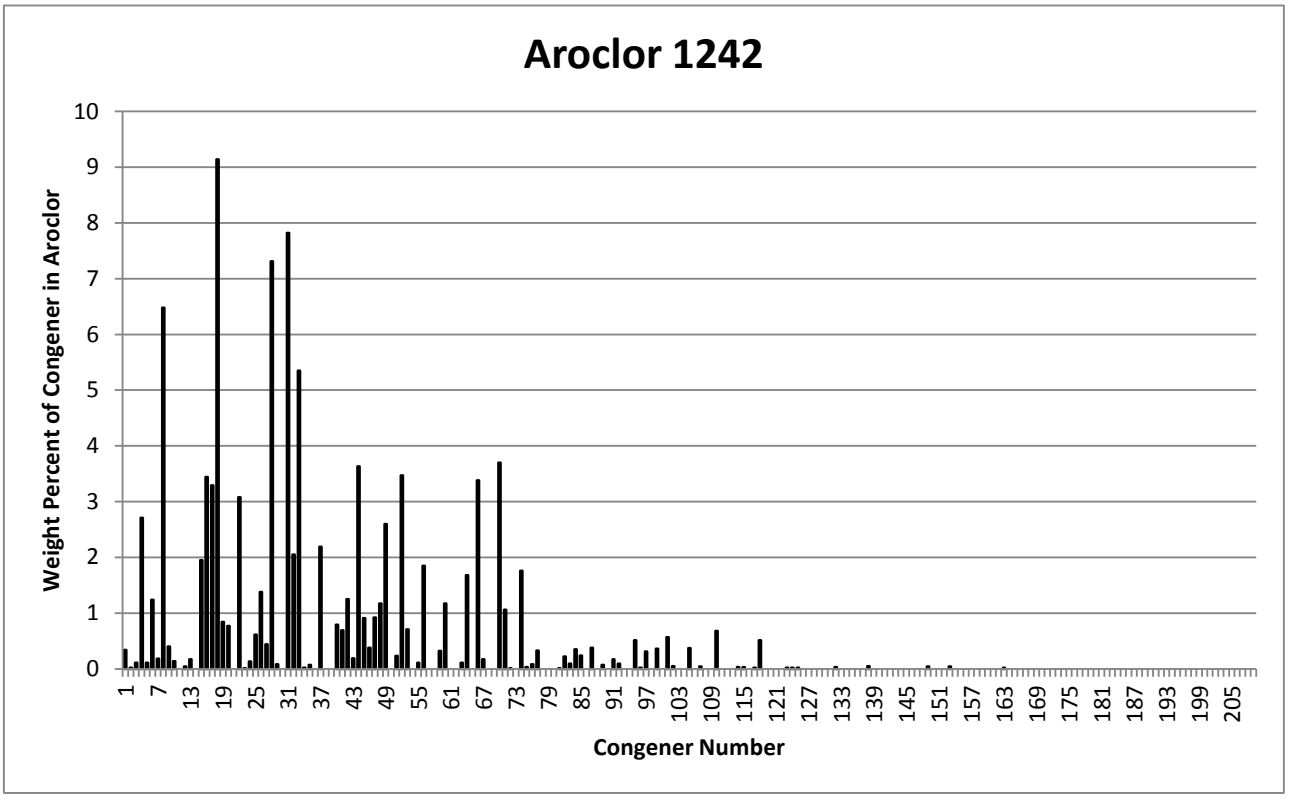
Adapted from ASTDR, 2000.

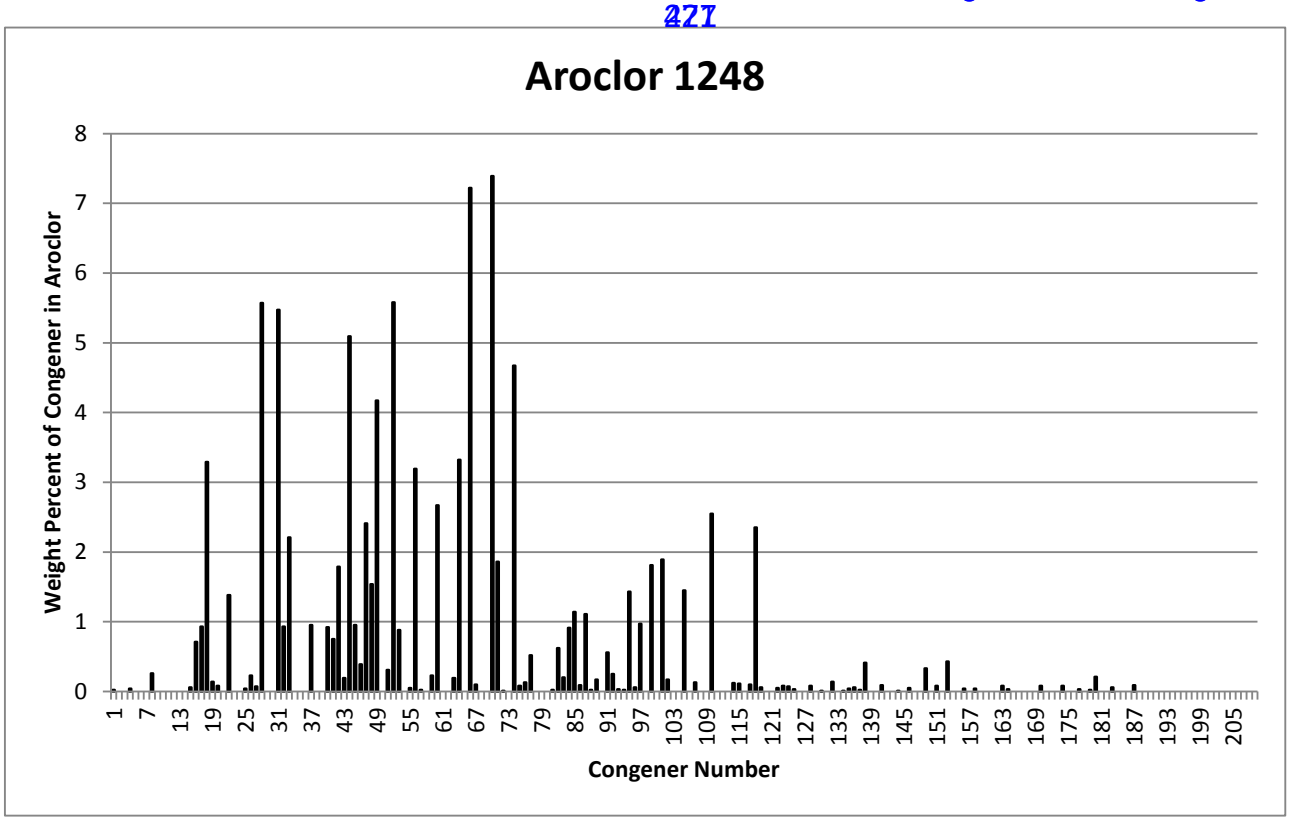
Weight Percent of Congeners in Aroclors

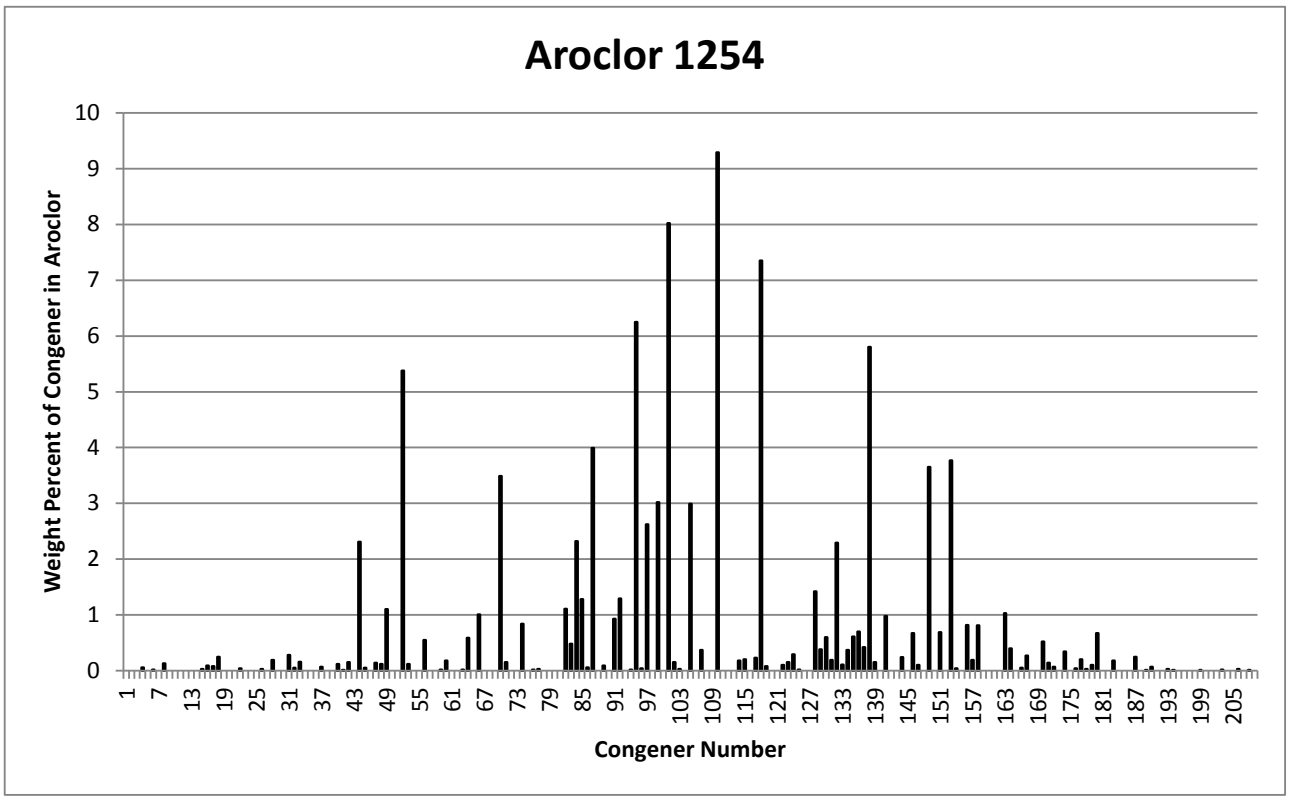


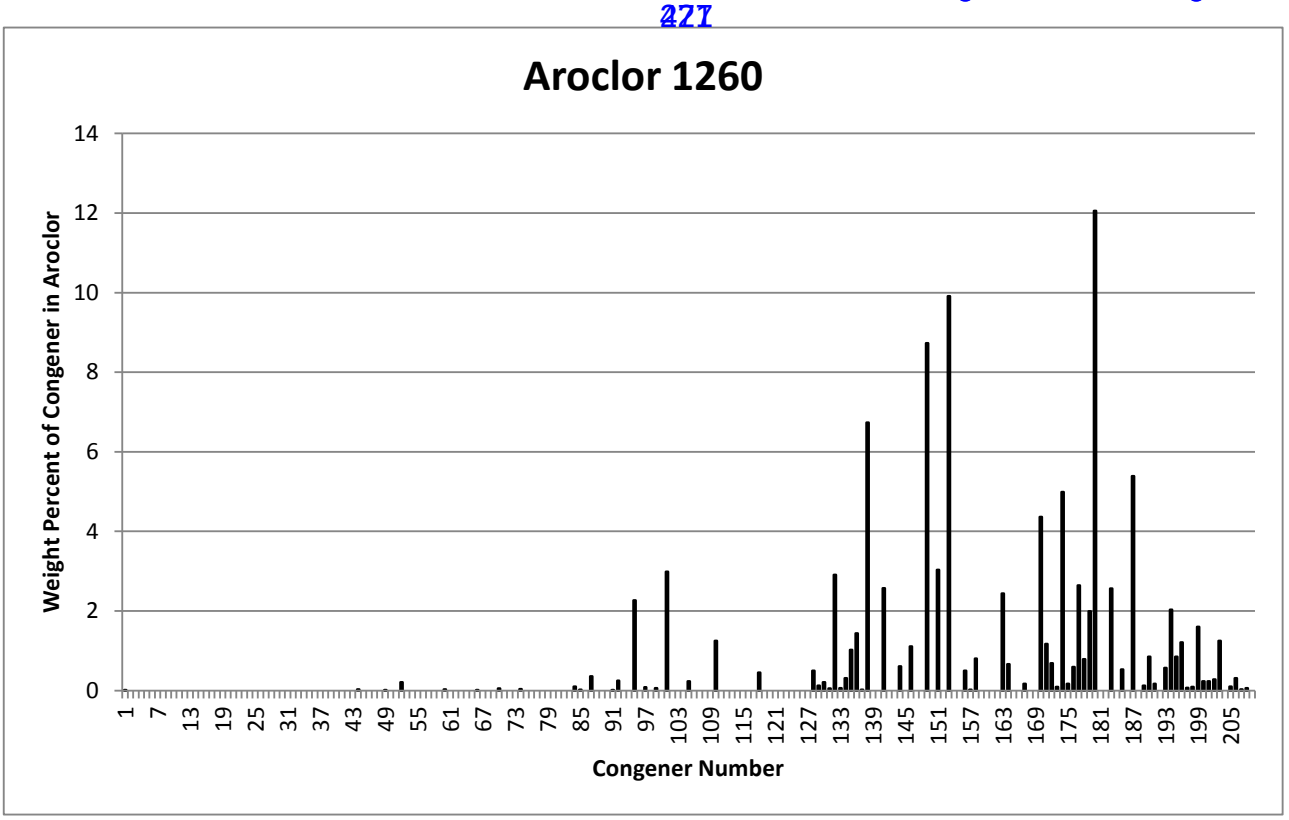


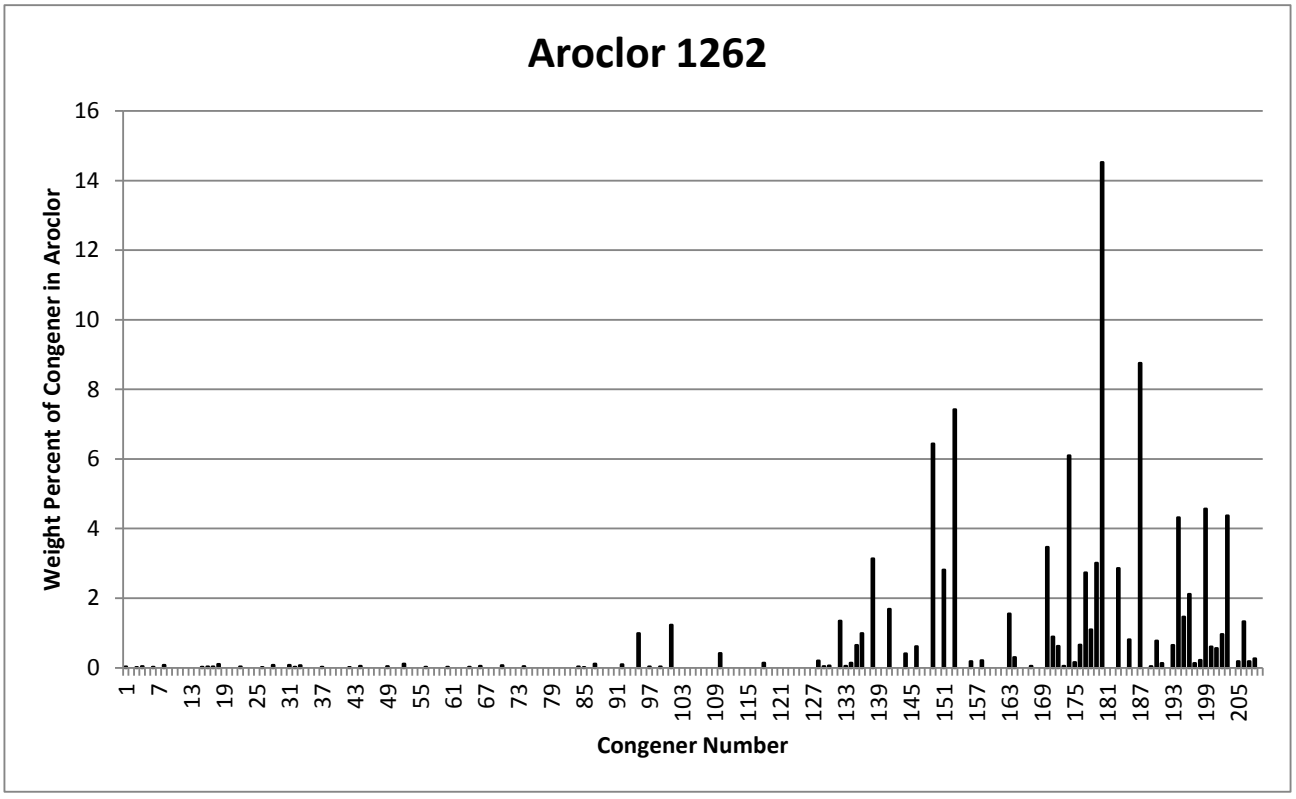

Aroclor 1016
Weight Percent of Congener in Aroclor
Congener Number


Aroclor 1242
Weight Percent of Congener in Aroclor
Congener Number


Aroclor 1248
Weight Percent of Congener in Aroclor
Congener Number


Aroclor 1254
Weight Percent of Congener in Aroclor
Congener Number


Aroclor 1260
Weight Percent of Congener in Aroclor
0
2
4
6
8
10
12
14
1 7 13 19 25 31 37 43 49 55 61 67 73 79 85 91 97 103 109 115 121 127 133 139 145 151 157 163 169 175 181 187 193 199 205
Congener Number


Aroclor 1262
Weight Percent of Congener in Aroclor
0
2
4
6
8
10
12
14
16
1 7 13 19 25 31 37 43 49 55 61 67 73 79 85 91 97 103 109 115 121 127 133 139 145 151 157 163 169 175 181 187 193 199 205
Congener Number

Appendix B

SUMMARY OF RESULTS

Table B-1

Summary of PCB Product Sampling Results

Product Type	Media	Product ID	Total PCB (ug/kg or ppb)	Field Replicate (ppb)	Lab Duplicate (ppb)	Brand
Yellow road paint	Liquid	001	0.732	2.686		Ennis standard #2 - Product # 983712
Yellow road paint	Liquid	002	64.880			Sherwin Williams Promar TM 5713
White road paint	Liquid	003	0.414	0.396		Ennis standard #2 - Product # 983711
White road paint	Liquid	004	0.281		0.220	Sherwin Williams Promar TM 5712
Hydrant Paint	Liquid/Spray	005	0.003		0.010	Rustoleum Pro HP Enamel - Aluminum
Utility Locate Paint	Liquid/Spray	006	21.527			Rustoleum Industrial Choice, Solvent-based - green
Class B Firefighting Foam	Liquid	007	0.029			Alcoseal 3-3 (AR-FFFP)
Deicer	Liquid	008	1.332	1.952		MgCl Freezegard
Deicer	Liquid	009	0.038			Enhanced salt brine with SB Boost
Vehicle wash soap	Liquid	010	0.003		0.068	SuperXL, Hotsy
Vehicle wash soap	Liquid	011	0.068			Simple Green
Pesticide/Herbicide	Liquid	012	<0.0001		<0.0001	2-4D: Nufarm Weedar 64
Pesticide/Herbicide	Liquid	013	6.890			Portfolio 4F, Wilbur-Ellis
Pesticide/Herbicide	Liquid	014	0.012			Roundup Pro Max, Monsanto
Pesticide/Herbicide	Liquid	015	0.316			Crosshair, Wilbur-Ellis
Motor oil	Liquid	016	0.856		0.826	SAE 15W-40 Firebird Heavy Duty EC (bulk), Connell Oil
Motor oil	Liquid	017	0.969			Valvoline Full Synthetic 5W-30
Used motor oil	Liquid	018	0.502	2.375		SAE 15W-40 Firebird Heavy Duty EC, Connell Oil
Diesel	Liquid	019	<0.019			#2 Diesel, dyed
Gasoline	Liquid	020	0.935		0.811	Regular unleaded
Dirt road dust suppressant	Liquid	021	0.091			Asphalt emulsions- EADA
Dirt road dust suppressant	Liquid	022	0.086			Lignosulfonate- Ligno Road Binder (natural polymer in wood)
Dirt road dust suppressant	Liquid	023	3.574			Dustguard Liquid MgCl (different concentration than deicer)
Lubricant	Liquid	024	0.623			MP Gear Lube SAE 85W-140, Phillips 66 Company
Asphalt tack	Liquid	025	0.085			SSR1 asphalt tack
Crack sealer	Solid	026	7.975			Special Asphalt SA Premier (3405- midrange crack sealer)
Asphalt release agent	Liquid	027	0.558		0.443	Soy What, TechniChem Corp.
Hydroseed	Solid	028	2,509.088			Natures Own Hydroseeding Mulch, Hamilton Mfg Inc
PVC pipe	Solid	029	1.999			ASTM 3034 8", Diamond PVC
CIPP liner	Solid	030	1.110			Cast in place pipe liner, installed by SAK
Shortliner	Solid	031	17.780			Infrastructure Repair Systems Inc
Yellow road paint, dried	Solid	032	0.565			Ennis standard #2 - Product # 983712
White road paint, dried	Solid	033	0.379		0.335	Ennis standard #2 - Product # 983711

Product Type	Media	Product ID	Total PCB (ug/kg or ppb)	Field Replicate (ppb)	Lab Duplicate (ppb)	Brand
Thermoplastic tape road striping	Solid	034	10.776			Ennis-Flint Pre-Mark
Antifreeze	Liquid	035	0.018			Kool Green Extended Life (recycled)
Thermoplastic tape road striping	Solid	036	3.325			Ennis-Flint Pre-Mark

Personal Care Products

Product Type	Media	Product ID	Total PCB (ug/kg or ppb)	Field Replicate (ppb)	Lab Duplicate (ppb)	Brand
Hand soap	Liquid	101	0.037			Dial Antibacterial, pomegranate and tangerine
Laundry soap	Liquid	102	0.174			Tide original liquid
Dish soap	Liquid	103	0.083			Dawn Ultra antibacterial
Shampoo	Liquid	104	0.058			Suave naturals
Toothpaste	Liquid	105	0.032			Aquafresh Extreme Clean Whitening

Notes:

Total PCB values have been blank corrected: congeners < 3 times the associated blank value not included in total.

ug/kg = micrograms per kilogram

ppb = parts per billion